Competitive exclusion products
EFSA Ad hoc hearing

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Remarks on regulatory discussions and current status

WHO (1994)

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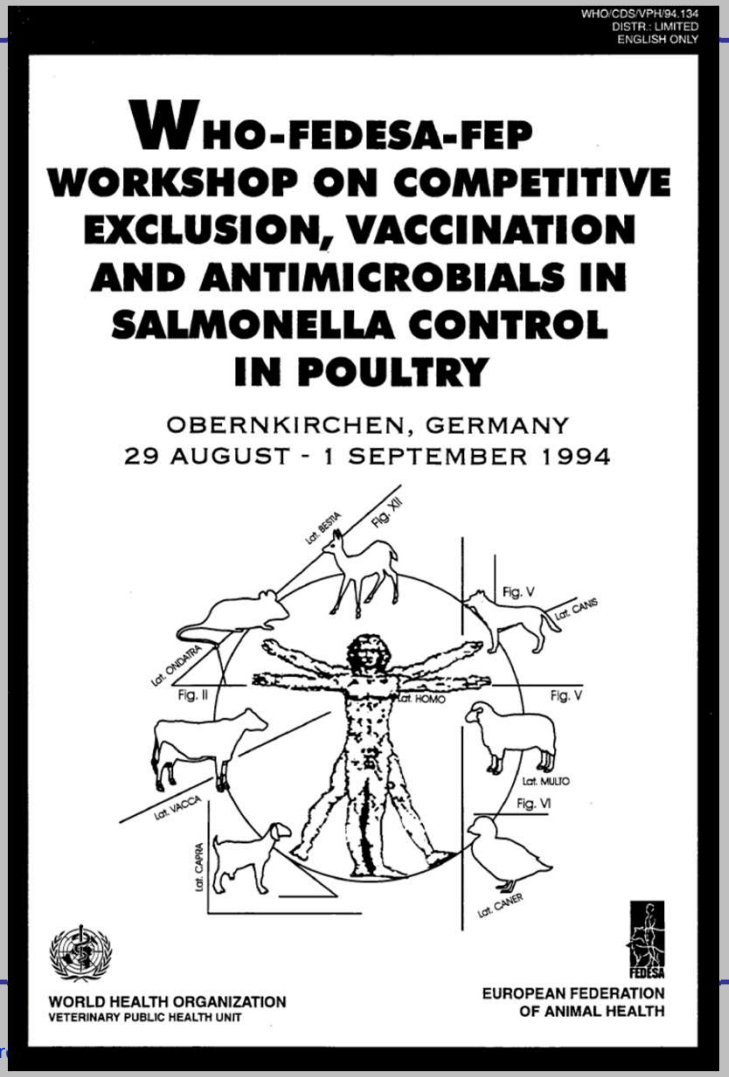
This report contains recommendations and suggestions for the use of antimicrobials, competitive exclusion (CE) products and vaccines as management tools to aid in reducing the incidence of Salmonella in poultry flocks, and in particular S. enteritidis and S. typhimurium (invasive serotypes).

5.2 Competitive exclusion (CE)

The use of normal gut flora for prophylactic purposes is only applicable at day 1 in the hatchery. CE should be administered by spraying the eggs at hatching. Ideally, CE should be given on day 1 and day 3 in the hatchery machines (days 19 and 21 of incubation). If treatment within the hatchery is not allowed, then CE may be sprayed in the containers used for transport. CE is most effective in hatcheries where the parent flocks are free from salmonellae, but it may be partially effective in the presence of a low level of infection.



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6. QUALITY ASSURANCE, SAFETY AND LEGAL ASPECTS

Since exclusion flora preparations cannot be defined in the same manner as either a vaccine or a veterinary medicinal product, WHO should recommend that the authorities create a special product category called "NORMAL GUT FLORA".

In relation to the avian intestinal tract, "normal gut flora" is an undefined preparation of live obligate and facultatively anaerobic bacteria originating from normal, healthy, adult individuals of an avian species, which is free from specific pathogenic micro-organisms and is quality controlled. The purpose of such a preparation is to compensate for any deficiencies in the composition of the normal intestinal microbiota that relate to the natural control of undesirable micro-organisms and arise from modern systems of poultry production.

"Normal gut flora", as defined above, should be distinguished from live "probiotics" which are preparations of only one or a few strains of micro-organisms, the primary purpose of which is to improve animal performance.

Regulatory status in the European Union

- No appropriate general category for competitive exclusion (CE) products, specifically when applied via spraying on animals
- Subject to national legislation
- National authorities may therefore tolerate such products under feed, accept it as a veterinary product, or in another category such as *competitive exclusion product*
- Some EU member states refused to authorize CE products
- 2001 review: CE products accepted for use in poultry in Finland, Denmark, Sweden. Norway, Ireland, the Netherlands, France, Spain and UK
- Currently authorized/tolerated in various EU member states

April - Juni 2001 **2/2001**, Seite 1 — Lohmann Information

„Competitive Exclusion" - ein Verfahren zur Prophylaxe der *Salmonella*-Infektion beim Geflügel

Dr. Ulrich Methner (Jena)

Einleitung

Der Gastrointestinaltrakt mit seiner Mikroflora stellt ein offenes ökologisches System dar. Die als „autochthon" bezeichnete normale Mikroflora des Darmes erfüllt nach dem derzeitigen Erkenntnisstand eine Reihe von Funktionen, die für den Wirtsorganismus von unterschiedlicher physiologischer Bedeutung sind:

1. Aufbau und Aufrechterhaltung einer mikrobiellen Barriere gegen die Ansiedelung und Vermehrung pathogener Erreger,
2. Förderung von Stoffwechsel und Durchblutung der Darmschleimhaut,
3. Beeinflussung des darmassoziierten Immunsystems,
4. Anregung der Darmmotilität,
5. Reduzierung der bakteriellen Translokation vom Darmlumen ins Lymphsystem,
6. Produktion von Vitaminen (SAVAGE, 1977).

Unter dem Verfahren der „Competitive Exclusion (CE)" versteht man die Applikation von Darmflora gesunder adulter Tiere an Küken kurze Zeit nach dem Schlupf bzw. in den ersten Lebenstagen. Diese Methode zur Reduzierung der intestinalen Salmonellenbesiedelung beim Geflügel wurde im Jahre 1973 durch NURMI und RANTALA beschrieben. Das nach den Beschreibern benannte „Nurmi-Konzept" bzw. der Begriff „Competitive Exclusion" werden als Termini für den Mechanismus der mikrobiellen Verhinderung der Besiedelung des Kükendarmes mit Salmonellen verwendet.

Es ist bekannt, dass die Empfänglichkeit von Küken für eine Infektion mit nicht wirtsadaptierten *Salmonella*-Serovaren mit steigendem Alter der Tiere abnimmt. Bereits MILNER und SHAFFER (1952) stellten die Beziehung zwischen dem Alter und der Dosis einerseits und dem Verlauf der *Salmonella*-Infektion nach oraler Applikation andererseits fest. Bei Eintagsküken genügten bereits 5 koloniebildende Einheiten (kbE) /Tier, um ein Haften der (NURMI und RANTALA 1973; SNOEYENBOS et al., 1982). Immunologische Reaktionen sind aufgrund der zum Zeitpunkt des Schlupfes der Küken nur unvollständig entwickelten Immunkompetenz (KODAMA et al., 1976; METHNER und STEINBACH, 1997; SHARMA, 1997) vermutlich erst bei älteren Tieren wirksam. Der Prozess der Etablierung der Darmflora variiert in Abhängigkeit von den Haltungs- und Fütterungsbedingungen und benötigt beim Dünndarm eine Zeit von etwa 2 Wochen während bis zum Abschluss der Mikrofloraentwicklung im Zäkum mehr als 4 bis 6 Wochen erforderlich sein können (BARNES et al., 1972, 1980). Der fehlende Kontakt der Küken zu den Elterntieren und die Haltung der Tiere in gereinigten und desinfizierten Ställen verzögern den Prozess der Darmfloraentwicklung. NURMI und RANTALA (1973) erkannten als erste diese Zusammenhänge und zeigten, dass durch die orale Applikation einer Suspension aus dem Kropf- und Darminhalt adulter gesunder Hühner an 1 bis 2 Tage alte Küken die Empfänglichkeit der Küken für eine 24 Stunden später erfolgende Infektion mit *Salmonella* Infantis wesentlich verringert werden kann. Damit wurde erstmalig gezeigt, dass die bei den älteren Tieren nachweisbar größere Widerstandsfähigkeit gegen eine Salmonella-Infektion auf die hochgradig empfänglichen Eintagsküken übertragen werden kann.

Die vorliegende Arbeit soll über Aspekte der Entwicklung des Verfahrens der „Competitive Exclusion" gegen *Salmonella*-Infektionen beim Geflügel informieren. Weiterhin sollen die Möglichkeiten und Grenzen des Einsatzes von Darmflorakulturen sowie Besonderheiten bei der Entwicklung von Kulturen definierter Zusammensetzung dargestellt werden.

Entwicklung von Competitive Exclusion-Kulturen nicht definierter Zusammensetzung

Nach den ersten erfolgreichen Versuchen unter Verwendung von Suspensionen aus dem Darminhalt adulter Tiere zur Vorbehandlung der Küken gegen eine *Salmonella*-Infektion wurde begonnen, den Zäkuminhalt unter anaeroben Bedingungen in flüssigen Medien zu kultivieren und

Standing Committee (21/22.09.2011)

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- Legal status of Broilact

  One Member State representative asked for clarification on the legal status of the oral use of Broilact, a product typically containing hundred(s) of different bacteria isolated from the caecum of healthy chicken. It had been mentioned that an application as a feed additive had already been rejected and that it is used in salmonella eradication measures in combination with vaccination. The outcome of the discussion was that the product is not an authorised feed additive and, considering its mode of action, cannot be considered a feed application.

Standing Committee (04/05.07.2024)

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A.03 Legal situation of the so-called 'competitive exclusion products' designed to be ingested via oral route

The presence on the market of so-called 'competitive exclusion products', used for the establishment and development of a 'normal' gut flora in some animal species, was brought to the attention of the Commission. Preliminary information on the nature, characterisation, route of administration, intended effect, etc. of such products was collected. The Commission is currently examining the legal situation of those so-called 'competitive exclusion products' that are designed to be ingested via oral route (including via spraying the product on the animals and/or their environment with a view to ensuring its subsequent ingestion), in particular vis-à-vis Regulation (EC) No 1831/2003 on feed additives.

Are CE products animal feed ?

- Used on food producing animals: 178/2002 (General Food Law) applies
- Are CE products feed additives?
  - Excluded from micro-organism definition (cf. Directive 95/11)
  - Not included when 1831/2003 and 429/2008 were discussed and adopted
  - Not covered by EFSA feed additive guidance (and not by draft MO guidance!)
- Definition of a feed additive
  - 'feed additives': substances, micro-organisms or preparations (not feed material/ premixtures, added to feed or water for one or more of the functions mentioned in Article 5(3)
  - 'micro-organism' means: colony-forming micro-organisms
- Decision in accordance with Article 2 (3) needed ?
  - Committee procedure to determine whether a substance, micro- organism or preparation is a feed additive

CE products as feed additives

- Risk assessment and risk management framework for feed additives did not consider/include CE preparations
- If feed additive, CE preparations should be evaluated and authorized considering their specific nature, properties and uses and not be «pressed» into the mould of other feed additive categories
- Adaption of framework necessary to accommodate to specifics of CE products

Challenges and limitations in the preparation of technical dossiers for competitive exclusion products as feed additives identified by the stakeholders

Policy & procedure

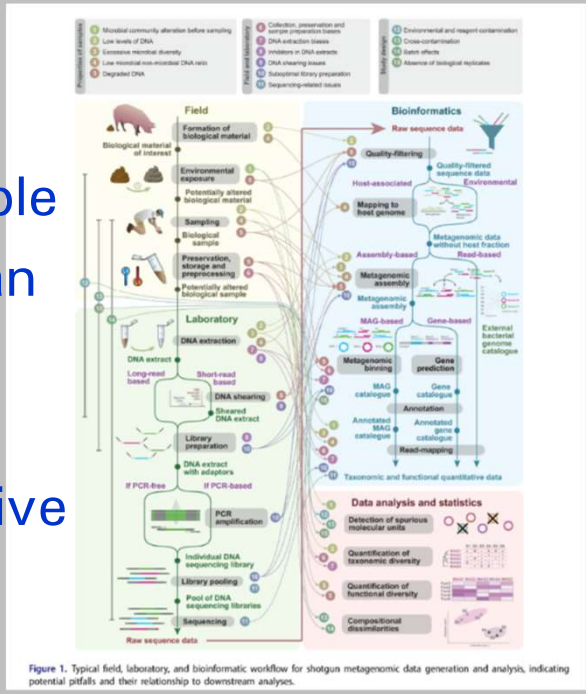
- Is *"appear to be compatible with the definition of feed additives"* a safe legal basis for classification as feed additive? For applicants, for EFSA?
- Level playing field: how to assure that data generation and submission is performed by applicants on an equal level?
- Stepwise approach – further consultations with EFSA before progressing from characterization to efficacy/safety before final submission
- Develop guidance jointly rather than post-submission ?
- Allocation to what functional group?

Characterization

- What is the active agent, are the active agents? The microbial community with its variability? Representative species? Marker?
- Characterization of the product as such vs its constituents
- Complex composition of broad range of bacteria:
  - How to develop specifications based on active agent(s)
  - Use representative species (colony forming units)?
  - Representative species could also be used to document the product variability and process manufacturing
- Challenge test against Salmonella as an alternative characterisation approach (requires animal testing)

Characterization

- Bacteria have not been isolated and defined, many not culturable – characterization at species/strain level difficult
  - Phenotypic characterisation between difficult and impossible
  - Antimicrobial production by a MO community different than by isolated strains
  - Toxigenicity, pathogenicity relevant?
- Deposition not possible for the additive itself, for representative species? What, how many? What is the purpose?
- Whole genome sequencing ? Shotgun metagenomics not standardized: sufficiently reliable for regulatory purposes, many open questions



Aizpurua et al 2024

Characterization

- Draft guidance (21.11.2024) revises data requirement for microoganisms
  - Data generation should be based on this document once adopted?
- How to discuss questions not addressed in this guidance?

Analytics & official control

- Product identification as the feed additive
  - Depends on agreed specifications
- Not used in compound feed
- Solution for spraying on chicks (1-time)

Safety

- Target animals: spraying application – what protocol to assess safety?
- Consumer safety: flora derived from chicken, specific assessment needed?
- Environmental safety: flora derived from chicken, occurring in the environment, not needed
- User safety: same as probiotics?

Efficacy

- Spray application, once after hatching: efficacy studies with this route of application – no protocols available, guidance focuses on feed/water inclusion
- Establishment of normal gut flora (support in …) – how to measure?
- Salmonella reduction/exclusion as an in vivo endpoint acceptable ?
- Challenge studies with microbes needed/acceptable?