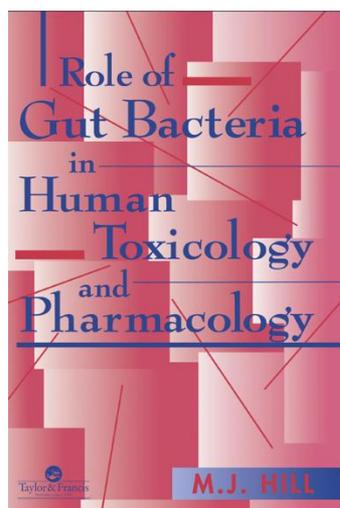
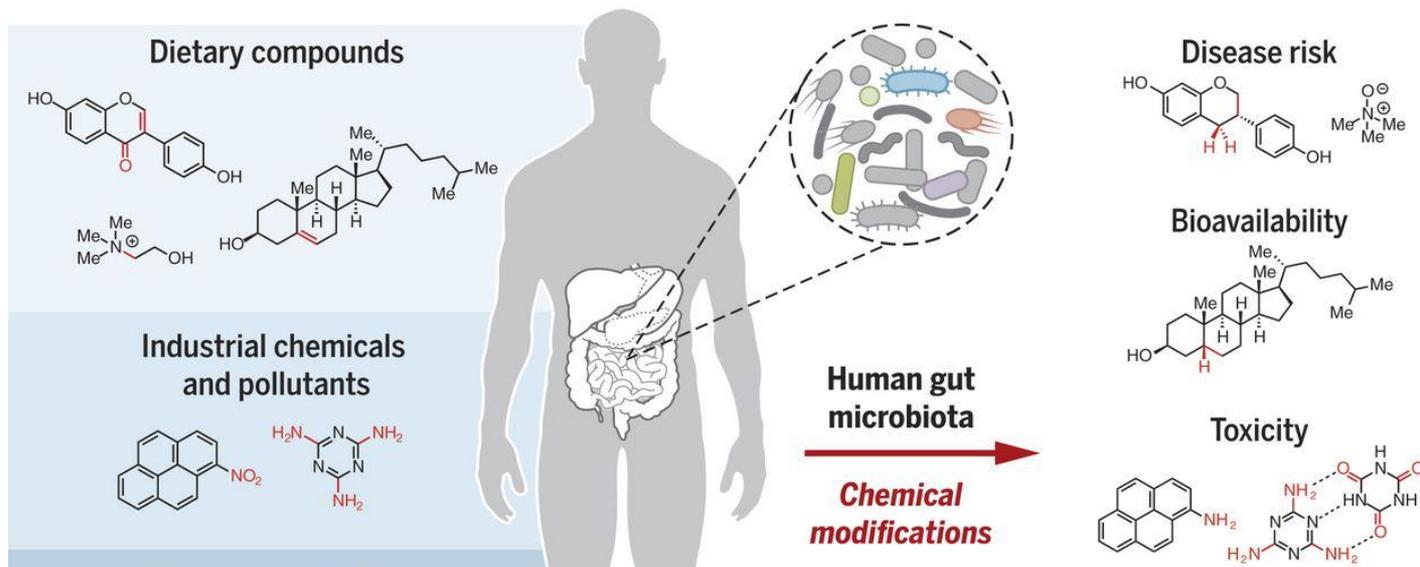


Effects of dietary exposures to pesticide residues on the gut microbiome

Robin Mesnage, PhD, King's College London, UK

London Microbiome Meeting 2019

The gut microbiota: a major player in the toxicity of environmental pollutants?



Recommended reading

Chemical transformation of xenobiotics by the human gut microbiota. Koppel (2017) *Science* 356, eaag2770.

Role of gut bacteria in human toxicology and pharmacology. By Bradley Hillman, 1995, CRC Press

What is a pesticide?

- Pesticides are chemical compounds that are used to kill insects, rodents, fungi and plants.
- They can be natural or synthetic.
- Plants generally produce compounds acting as pesticides to protect themselves against herbivores and insect attacks.
- Synthetic pesticides are vastly inspired from natural pesticides which have been modified to be more stable, more specific, and more toxic



Some synthetic insecticides have health effects in agricultural workers or following domestic applications

Sagiv et al., 2019. PNAS. 116 (37) 18347-18356

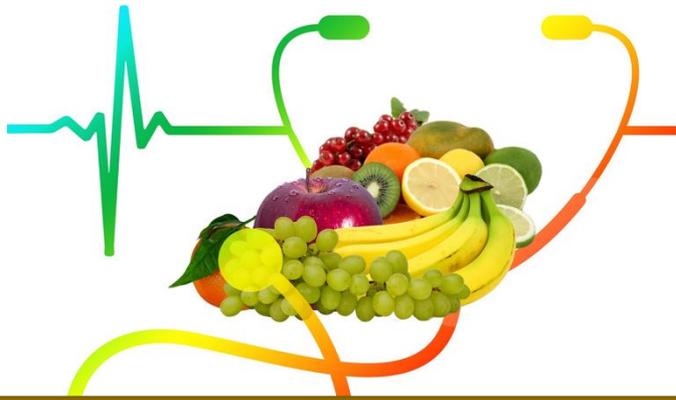
Larsen et al., 2017 Nature Communications 8, Article 302

Cognez et al, 2019 Occup Environ 76(9):672-679.



Little is known about the effects of long-term exposures to dietary pesticide residues

Are organic food consumers healthier?



Increased organic food consumption

sufficient evidence

Decreased exposure to synthetic pesticides

insufficient evidence

Health benefits

sufficient evidence

Organic food consumer demographic and lifestyle covariates

More education
Less smoking
More physical activity
Healthier dietary choices
Placebo effect of marketing

The gut microbiome is a mediator of insecticide resistance

- *Enterococcus* sp. enhanced resistance to the insecticide chlorpyrifos in the diamondback moth

Xia et al (2018) Front. Microbiol. 9:25.



- Fenitrothion-degrading *Burkholderia* strains in bean bug *R. pedestris*

Kikuchi et al (2012) PNAS 109:8618-22



- *Drosophila melanogaster* gut-derived *Lactobacillus plantarum* metabolize chlorpyrifos and affects its toxicity

Daisley et al., (2018) Appl Environ Microbiol. 84(9).



Gut microbiota mediate caffeine detoxification in the primary insect pest of coffee



Pseudomonas species subsist on caffeine as a sole source of energy

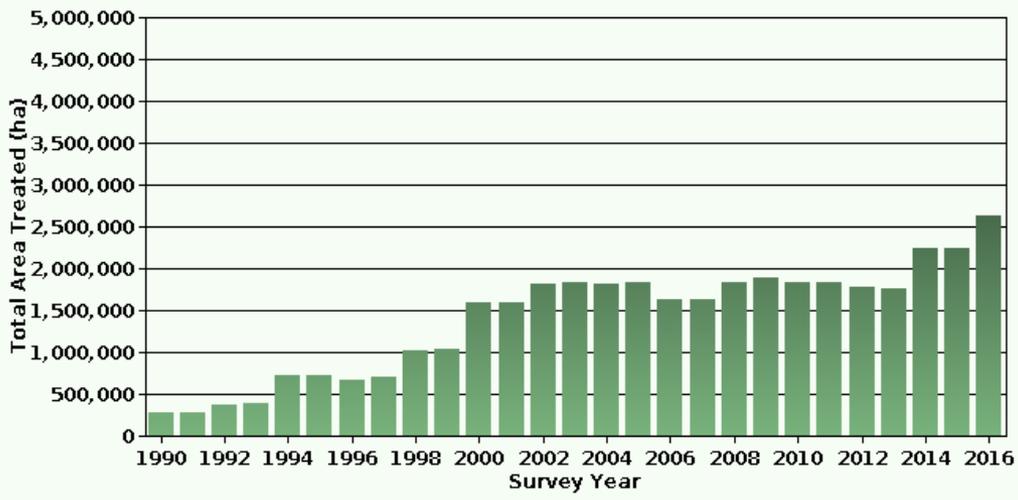
Perturbation of the gut microbiome may contribute to the neurotoxicity of organophosphate pesticides

Roman et al., 2019. NeuroToxicology 75, Pages 200-208

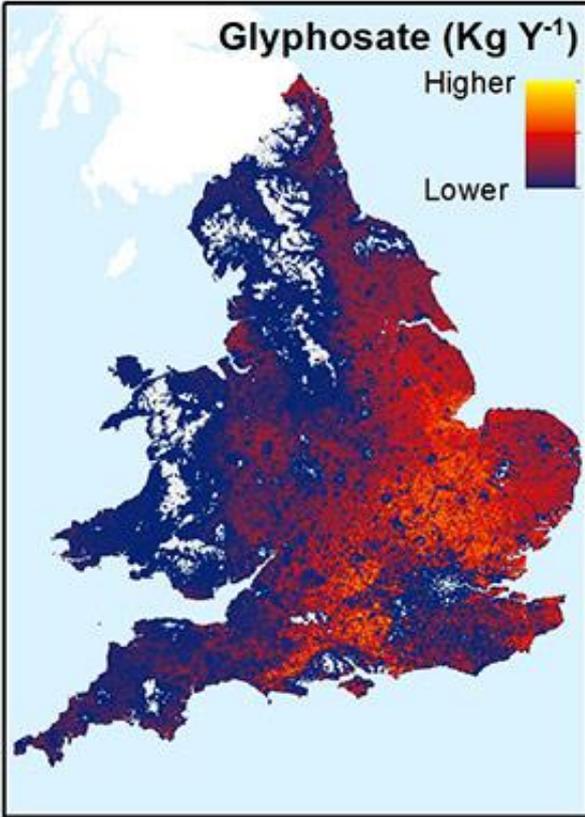
- In rats or mice, no human study
- High doses, unrealistic
- Effects are secondary to systemic effects
- Mostly using 16S rRNA sequencing
- More studies are needed to reflect real-life exposure scenarios

Glyphosate-based herbicides are the most heavily applied herbicide in the world and usage continues to rise

Human exposures to glyphosate are rising



<https://www.fera.co.uk>



<https://www.ceh.ac.uk>

Does glyphosate pose risks to human health?

Glyphosate is frequently found in the food chain because it is directly sprayed on edible crops

It is sprayed on cereals before the harvest to accelerate ripening, or to clear weeds during cultivations of Roundup-tolerant genetically modified crops

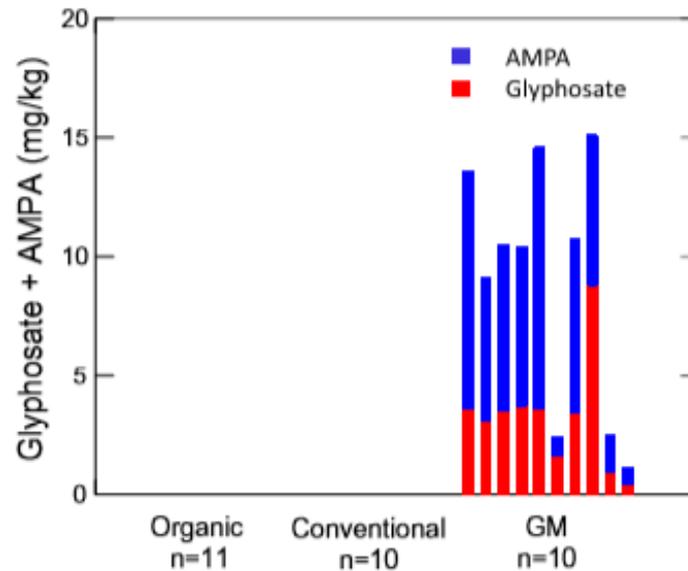


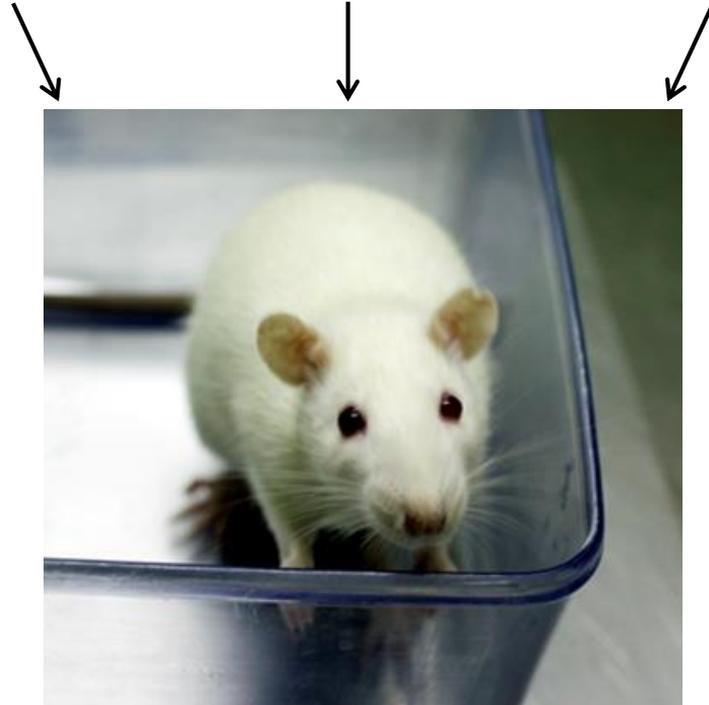
Fig. 1. Residues of glyphosate and AMPA in individual soybean samples (n = 31).



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Can glyphosate affect the gut microbiome?

Tap water (0.5, 50 and 175 mg/kg bw/day) Glyphosate (0.5, 50 and 175 mg/kg bw/day) MON52276 (0.5, 50 and 175 mg/kg bw/day)



90 days

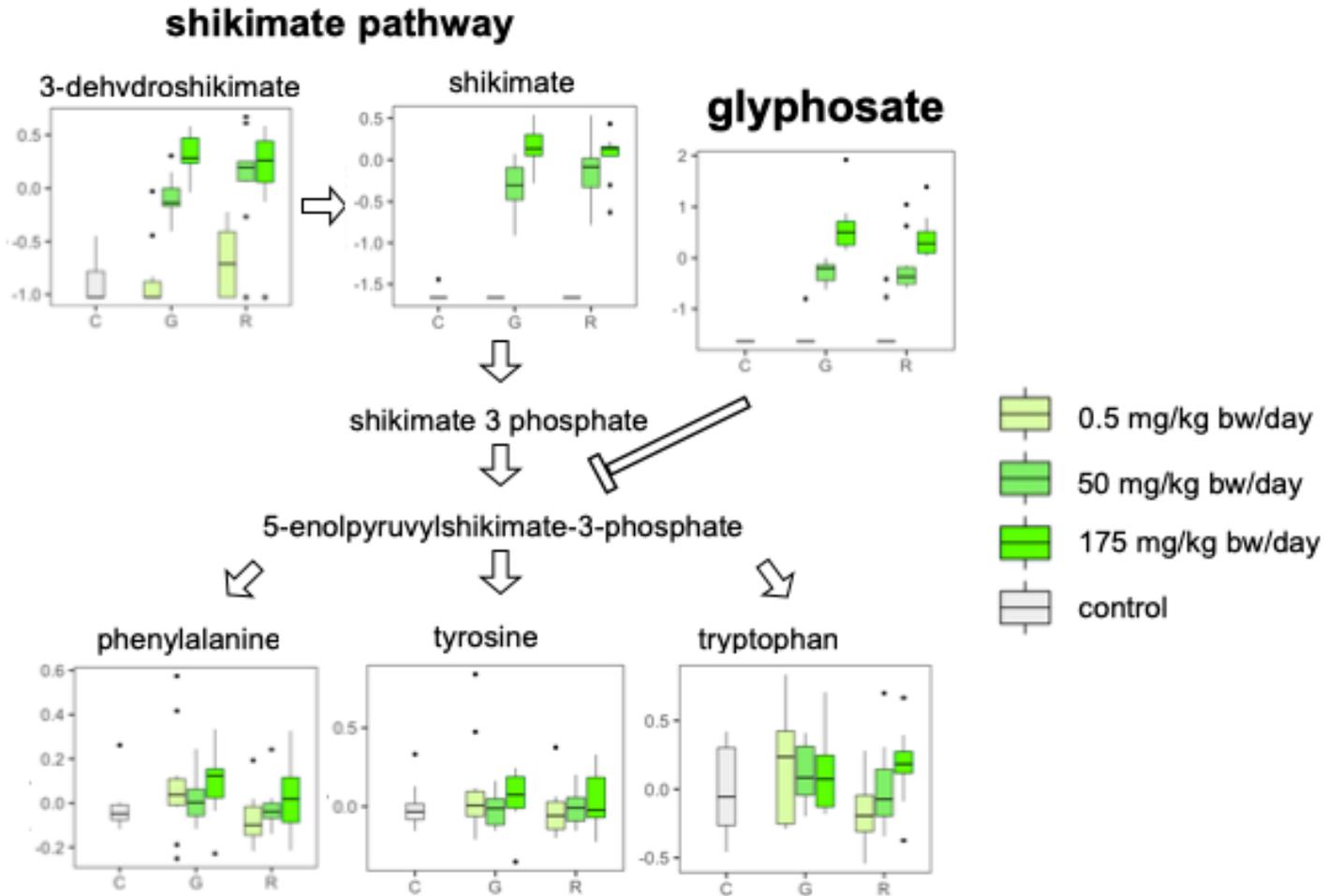
X12 per group

Gut microbiome
Caecum metabolomics
Caecum metagenomics

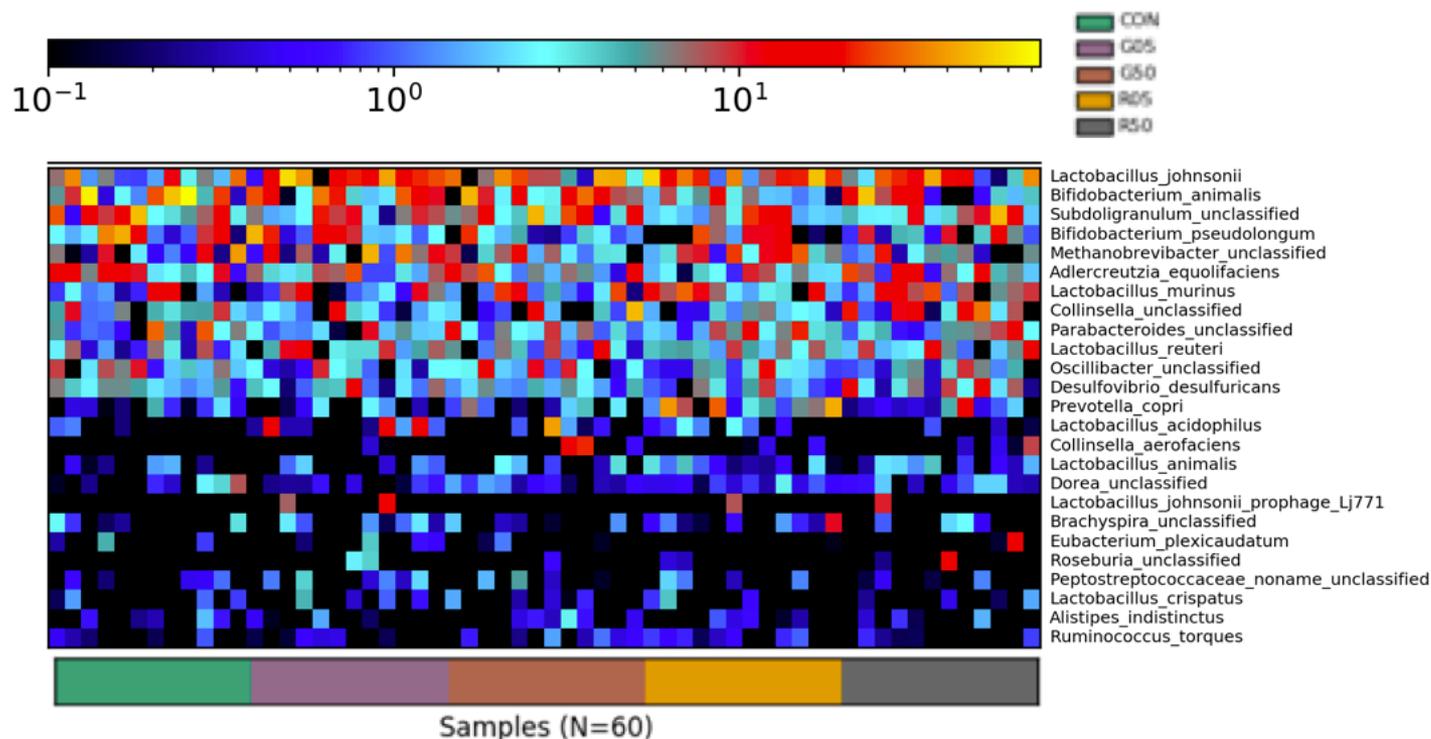
General toxicity
Liver and kidney histopathology
Biochemistry
Serum metabolomics

Liver molecular profiles
Transcriptomics
Methylation profiles

Caecal metabolomics reveals that glyphosate inhibits the EPSPS pathway in the rat gut microbiome



Analysis of shotgun metagenomics data



Data analysis with Metaphlan2 and Humann2 did not reveal effects of glyphosate, a new analysis using a gene catalogue of the Sprague-Dawley rat gut metagenome is ongoing

Evaluating the effects of synthetic pesticide exposure through analysis of the faecal microbiome in twins discordant for organic food consumption.



Exposure to 571 synthetic pesticides in 65 twin pairs

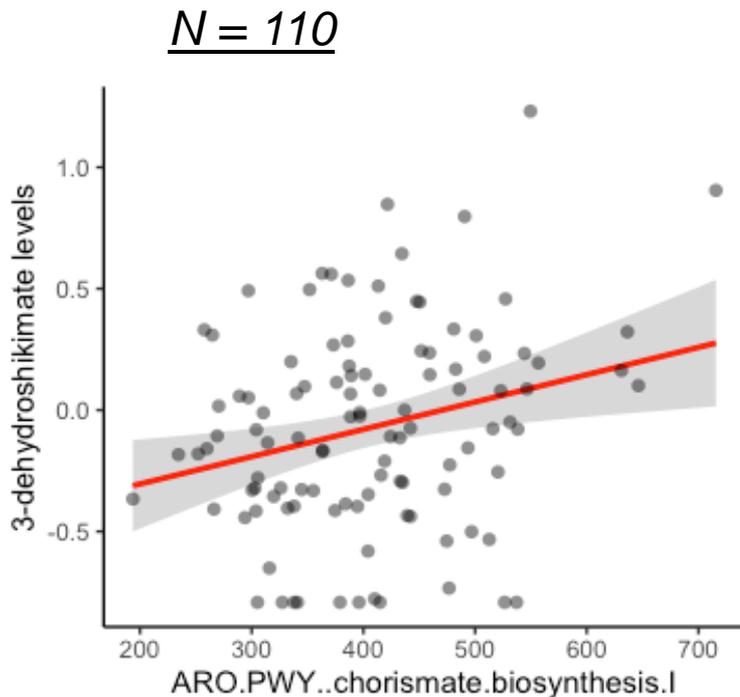
Data from pilot study



Urinary analysis of pesticide residues in 5 twin pairs reveals exposure to the herbicide glyphosate in British individuals

ID	Glyphosate ($\mu\text{g/L}$) (LD = 0,4 $\mu\text{g/L}$)
01	< LD
02	8.7
03	4.9
04	10.1
05	24.2
06	11.71
07	2.5
08	6.7
09	12.6
10	12.9

Faecal samples in 65 twin pairs that are discordant for an organic diet are studied by shotgun metagenomics and metabolomics to understand if pesticide exposure associates with changes in the faecal microbiome



Ongoing analysis

3-dehydroshikimate acid level correlate with metagenome composition

Can glyphosate exposure affect 3-dehydroshikimate acid level in the human faecal microbiome?

Next steps?

- 1/ Completing the study of associations between pesticide exposure and faecal microbiota composition
- 2/ Can organophosphate exposure be associated with changes in gut microbiome composition?
- 3/ Evaluation of the metatranscriptome in rats exposed to glyphosate
- 4/ Evaluate if an increase in shikimic acid levels can have health consequences

**Thank you research
Collaborators!**

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Thank you for your attention!
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