Case Study B
Pain Relief Medication

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Case statement

- 20 experiments on mice with combinations of marijuana and morphine, of which:
  - 1 control experiment;
  - 5 experiments with marijuana only;
  - 8 experiments with morphine only;
  - 6 experiments with both drugs.
- 10 mice used per experiment;
- Each mouse undergoes a tail flick test.

The tail flick test assesses the effect of drugs on the mouse.

In each experiment, the proportion of mice not flicking their tail can be interpreted as a **measure of the effect of the drug** for the chosen experimental dosage.

First objective

Determine the minimum dosage amount of the drugs that achieves **efficacy**.

The dosage of a drug is said to be **efficient** if at least 50% of the subjects are responding.

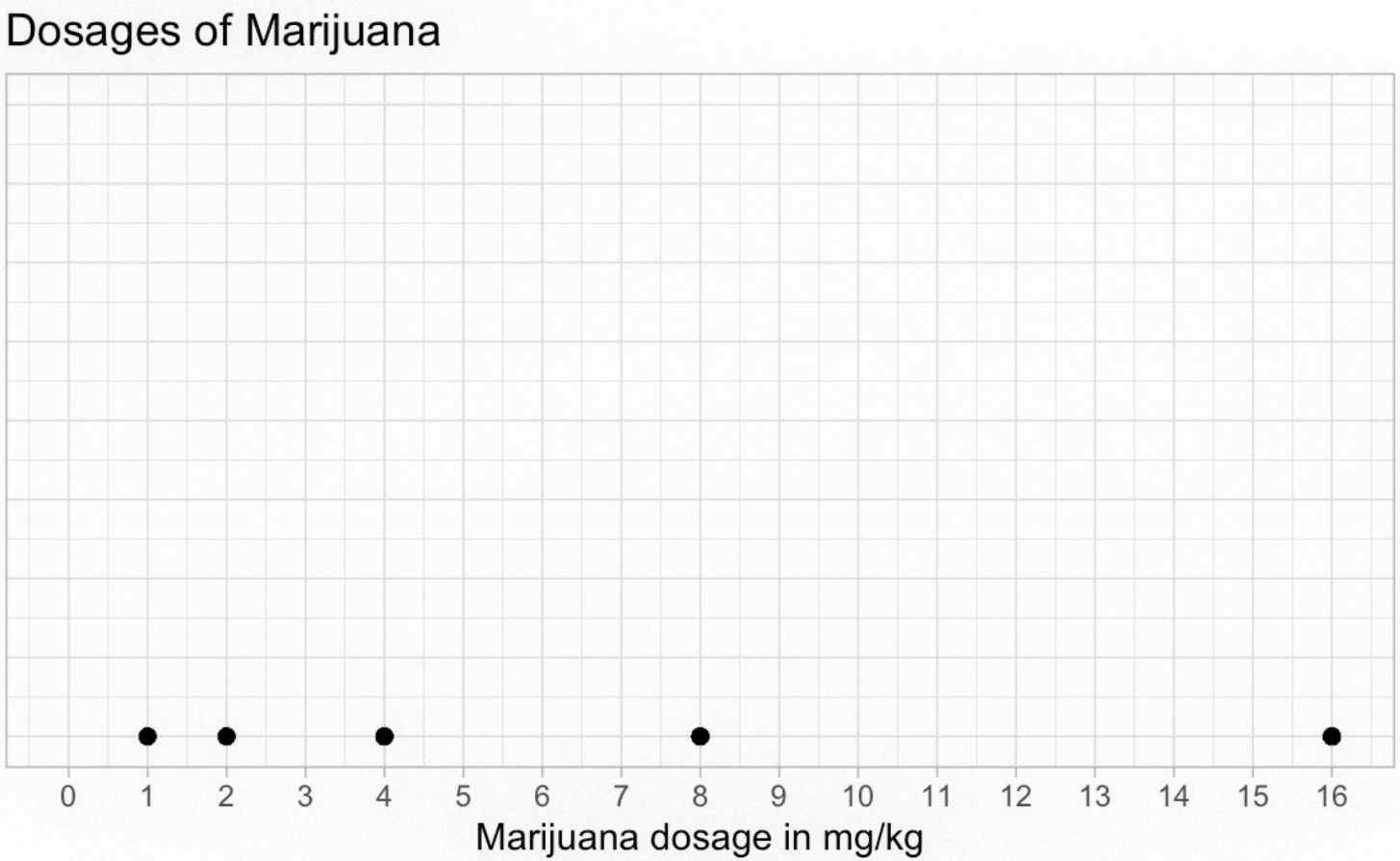
Second objective

Detect whether a **synergy** *exists between the two drugs.*

If the combined efficacy of the two drug dosages is greater than the sum of the individual efficacy of each drug for its respective dosage, there is **synergy**.

Identifying synergy with the isoboles method

The isoboles method is a graphical representation which allows to identify synergy and helps to better understand the concept.


Dosages of Marijuana
0
1
2
3
4
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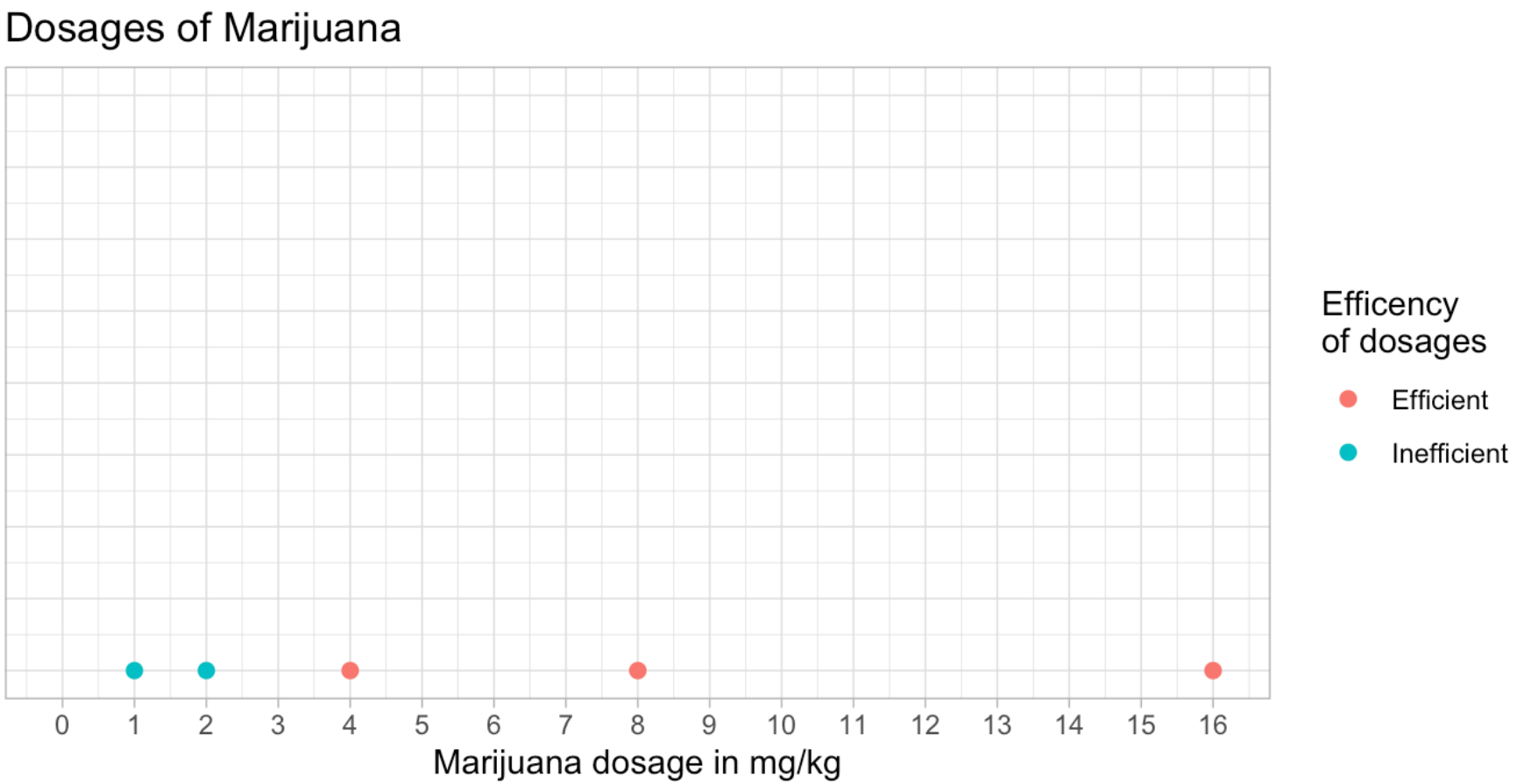
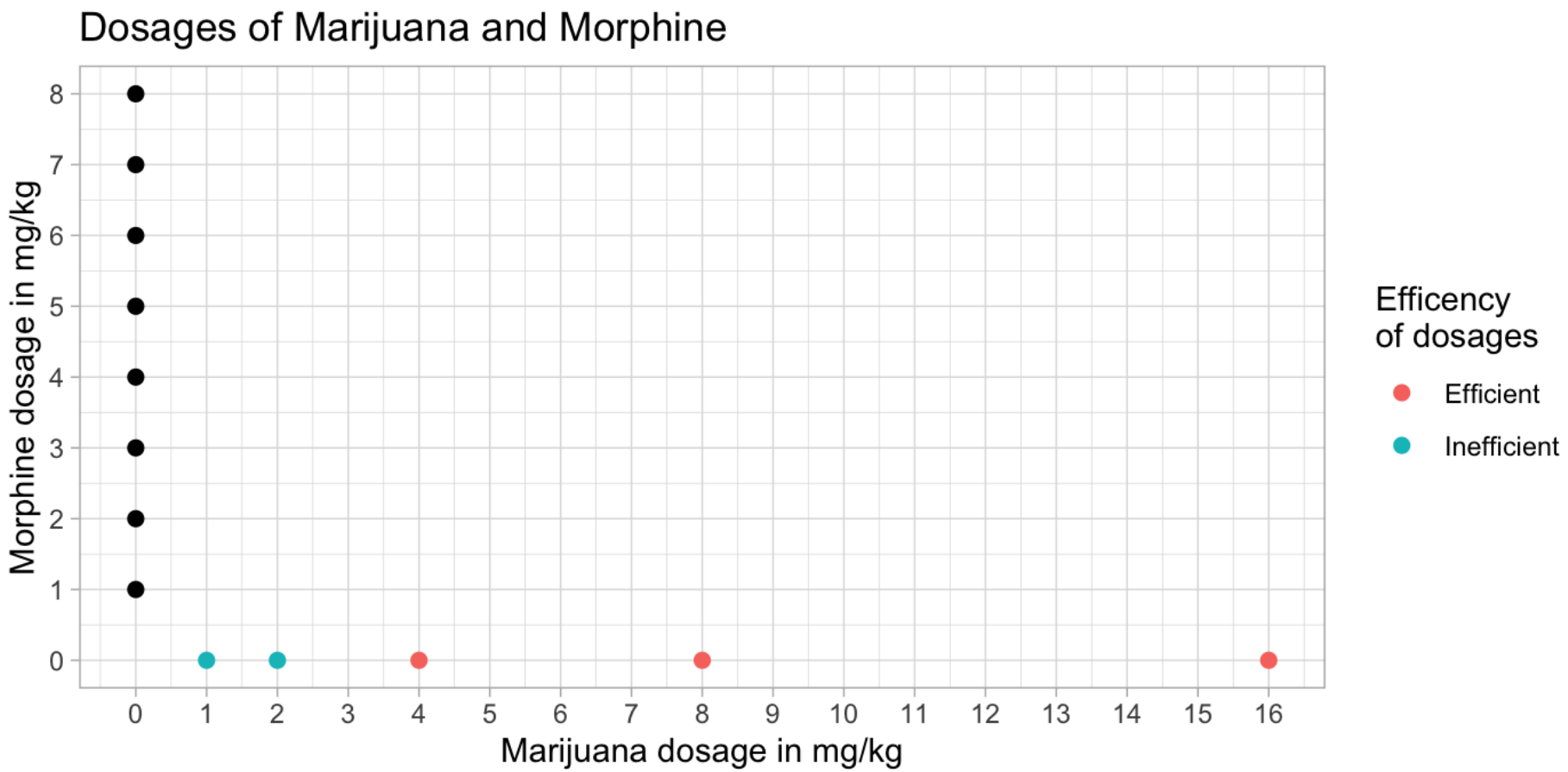
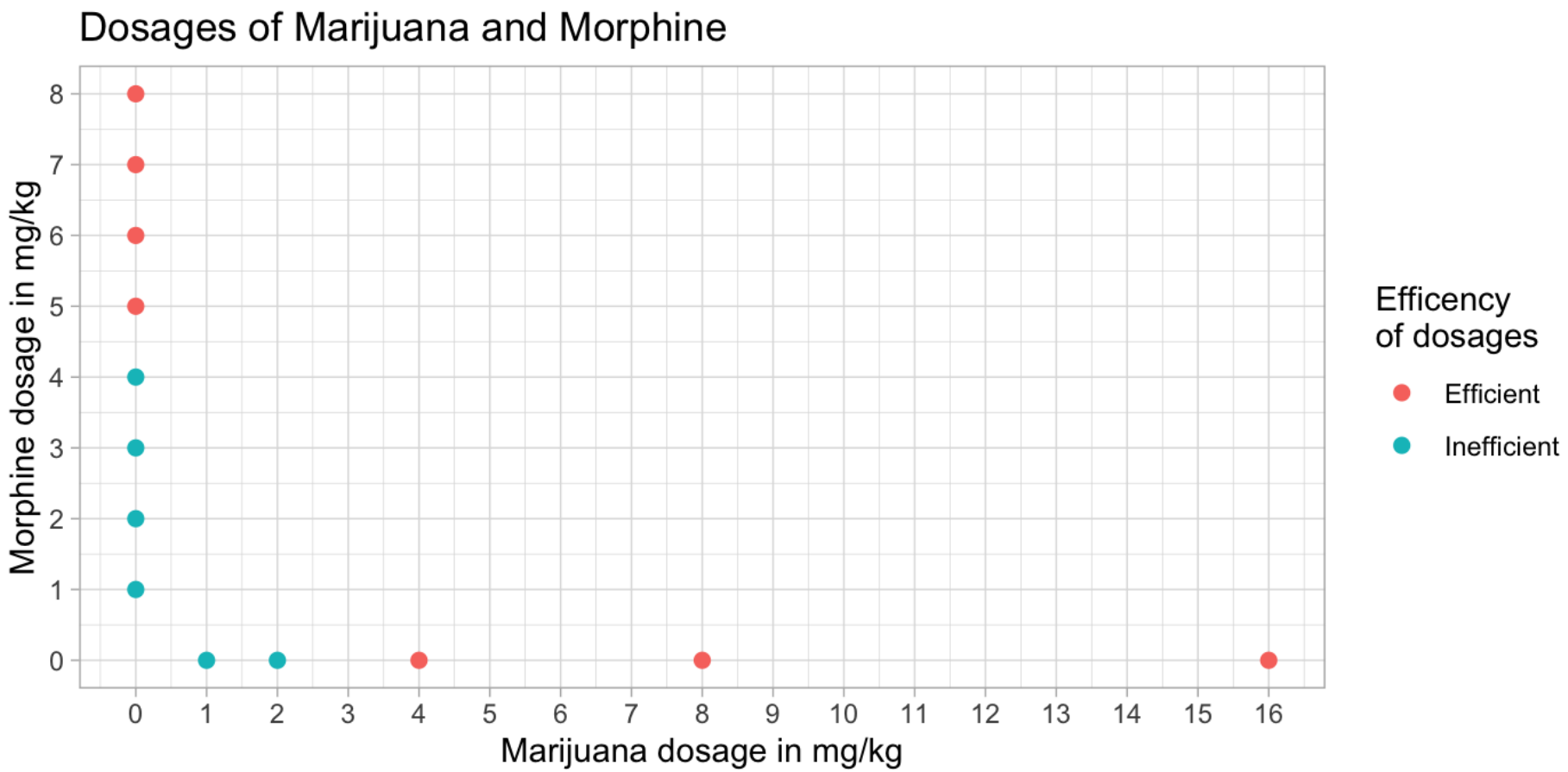
15
16
Marijuana dosage in mg/kg


Dosages of Marijuana
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
Marijuana dosage in mg/kg
Efficency of dosages
Efficient
Inefficient


Dosages of Marijuana and Morphine
Morphine dosage in mg/kg
0
1
2
3
4
5
6
7
8
Marijuana dosage in mg/kg
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
Efficency of dosages
Efficient
Inefficient


Dosages of Marijuana and Morphine
Morphine dosage in mg/kg
0
1
2
3
4
5
6
7
8
Marijuana dosage in mg/kg
0
1
2
3
4
5
6
7
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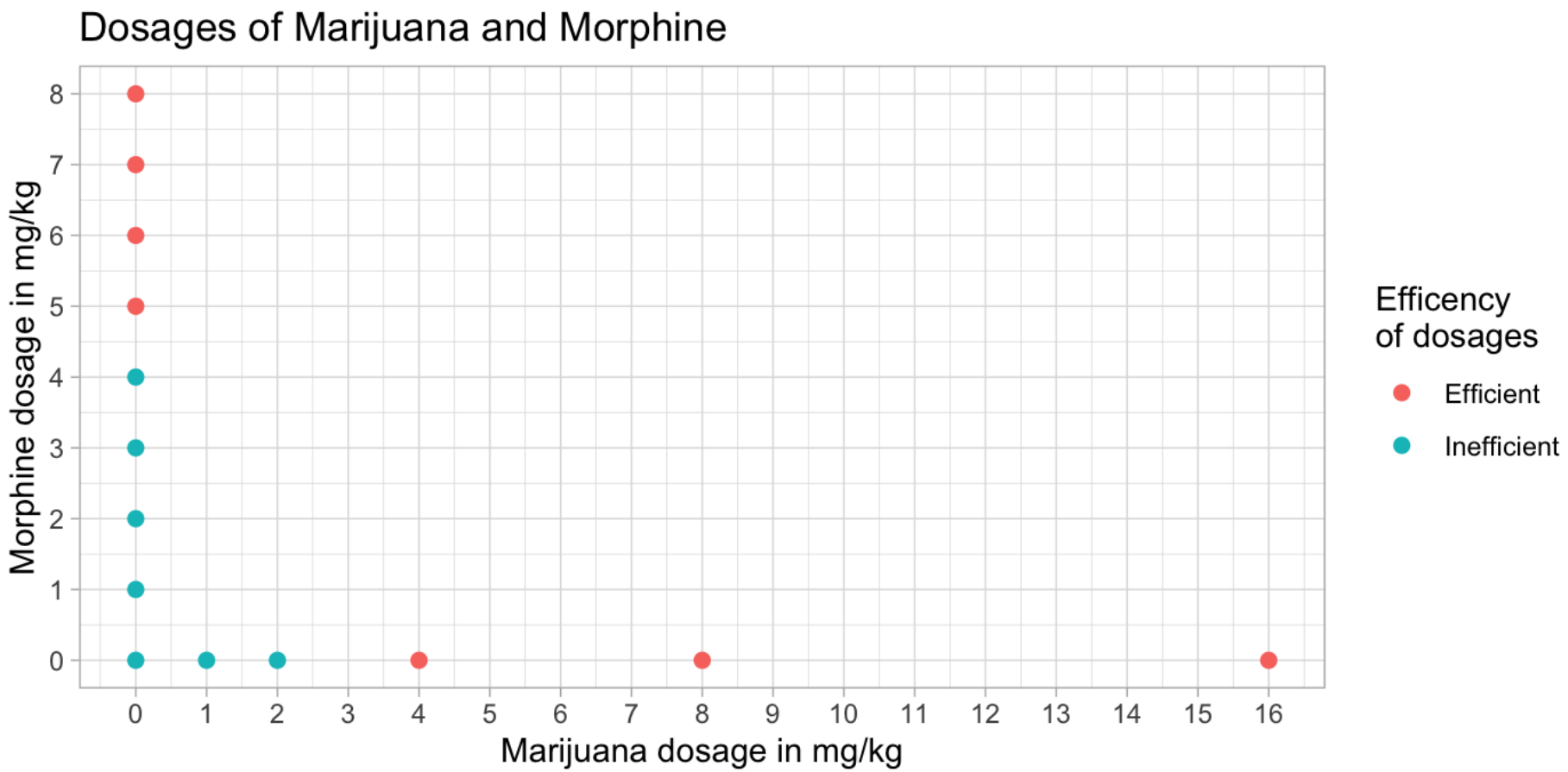
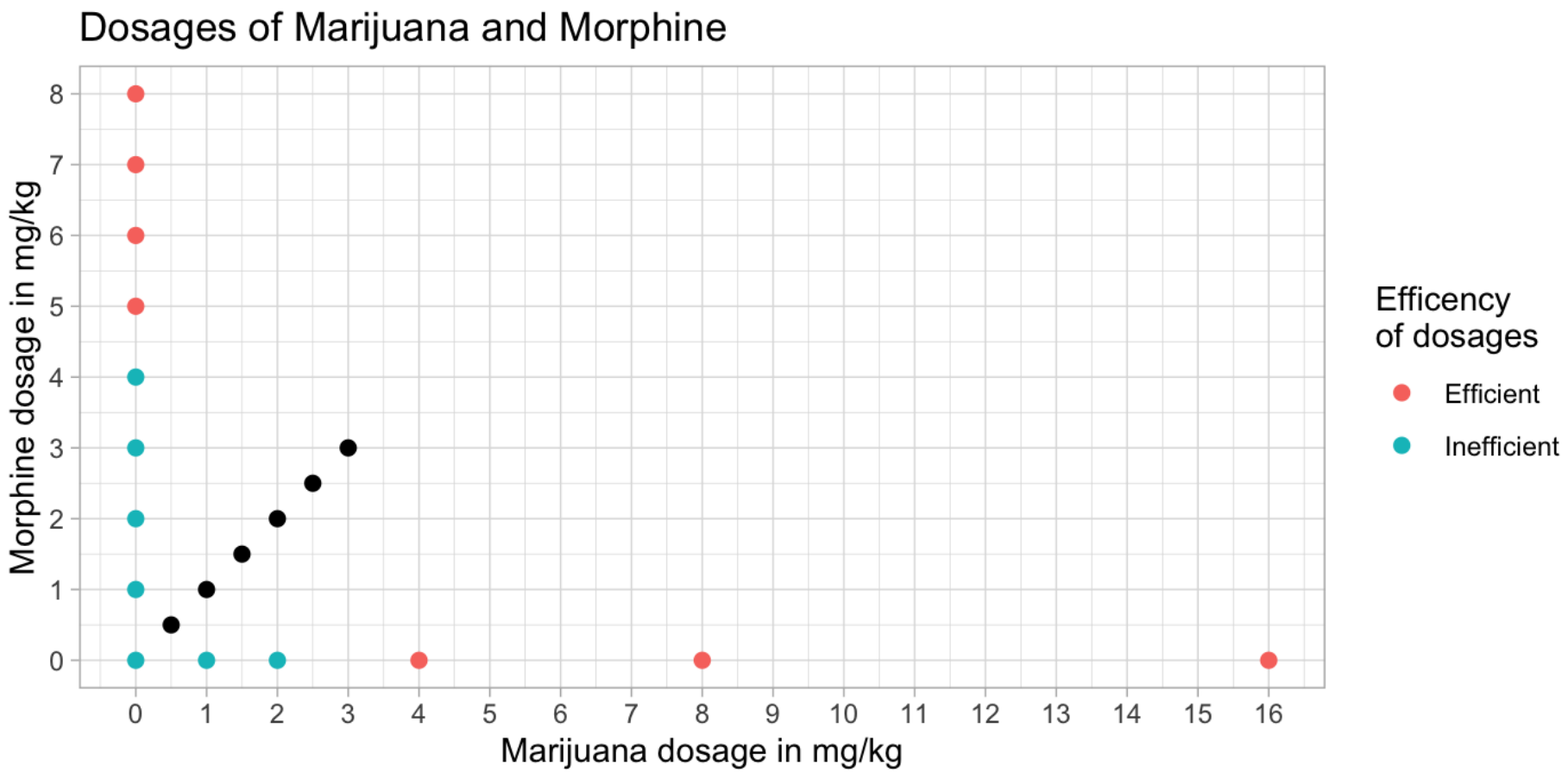
11
12
13
14
15
16
Efficency of dosages
Efficient
Inefficient


Dosages of Marijuana and Morphine
Morphine dosage in mg/kg
0
1
2
3
4
5
6
7
8
Marijuana dosage in mg/kg
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
Efficency of dosages
Efficient
Inefficient


Dosages of Marijuana and Morphine
Morphine dosage in mg/kg
0
1
2
3
4
5
6
7
8
Marijuana dosage in mg/kg
0
1
2
3
4
5
6
7
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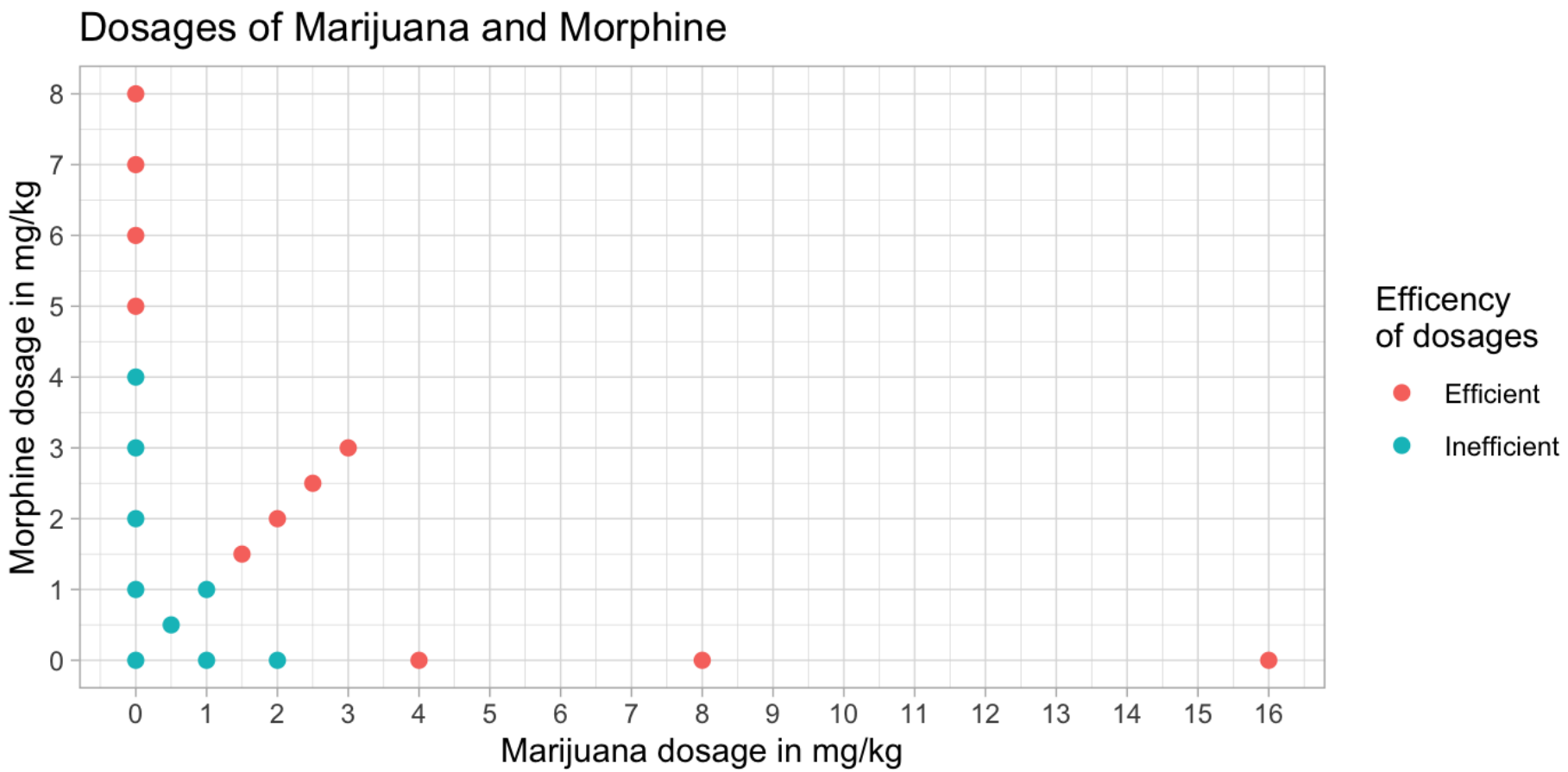
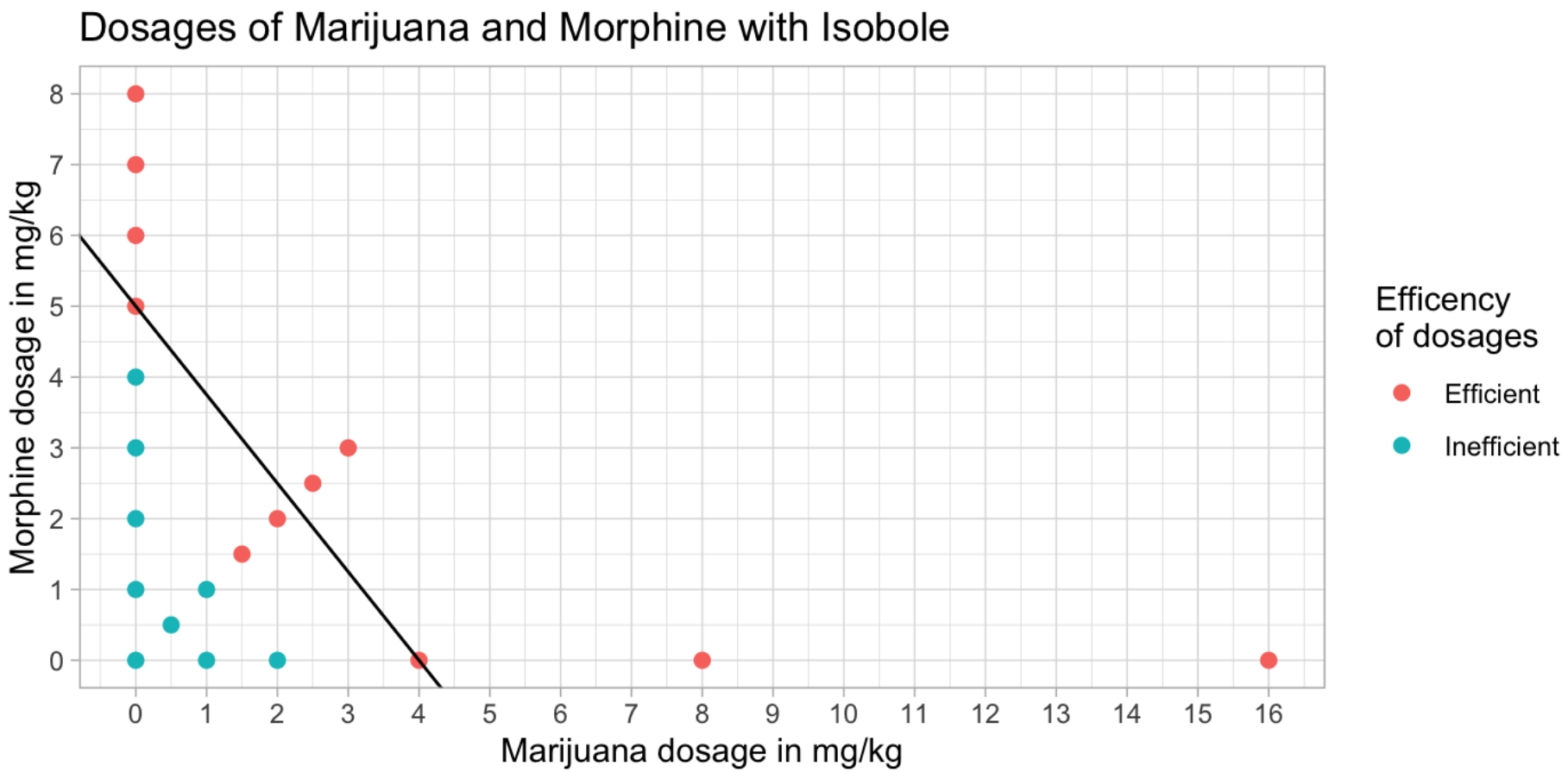
9
10
11
12
13
14
15
16
Efficency of dosages
Efficient
Inefficient


Dosages of Marijuana and Morphine
Morphine dosage in mg/kg
0
1
2
3
4
5
6
7
8
Marijuana dosage in mg/kg
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
Efficency of dosages
Efficient
Inefficient


Dosages of Marijuana and Morphine with Isobole
Morphine dosage in mg/kg
0
1
2
3
4
5
6
7
8
Marijuana dosage in mg/kg
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
Efficency of dosages
Efficient
Inefficient

Isobole insights

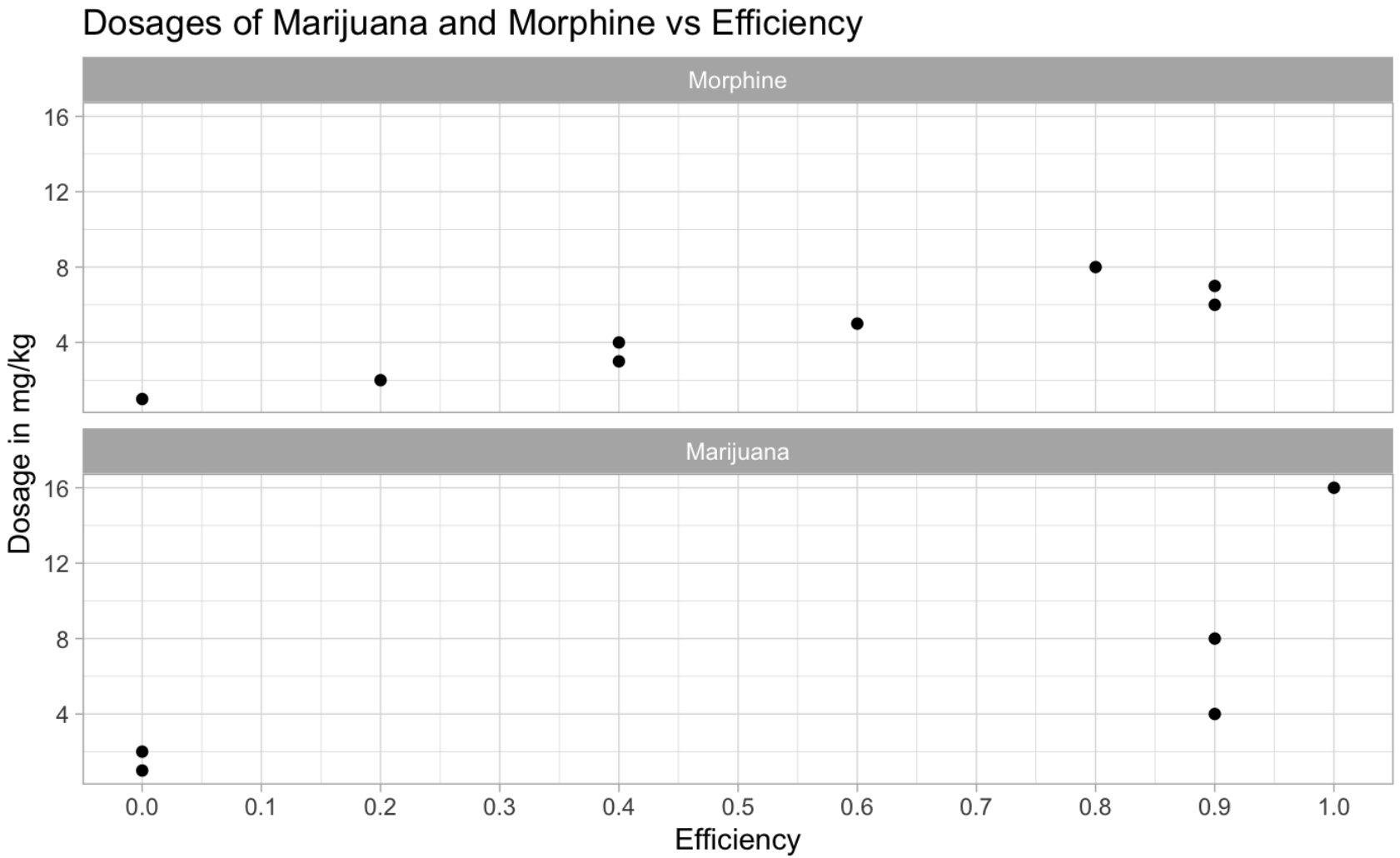
- Using 4 mg/kg of marijuana gives an equivalent effect ($\geq$ 50% of mice responding) to using 5 mg/kg of morphine.
- Combined dosages of the two drugs which are on the isobole have an equivalent effect to the ones mentioned above.
- A combined dosage which is under the isobole but is still efficient is synergic.

Isobole conclusion

- ✓ **First objective, minimal efficient dosage:**
  - 4.0 mg/kg for marijuana alone;
  - 5.0 mg/kg for morphine alone;
  - 1.5 mg/kg of each for both drugs.
- ✓ **Second objective, synergy:**
  Dosages of 1.5 mg/kg and 2.0 mg/kg each are synergic.

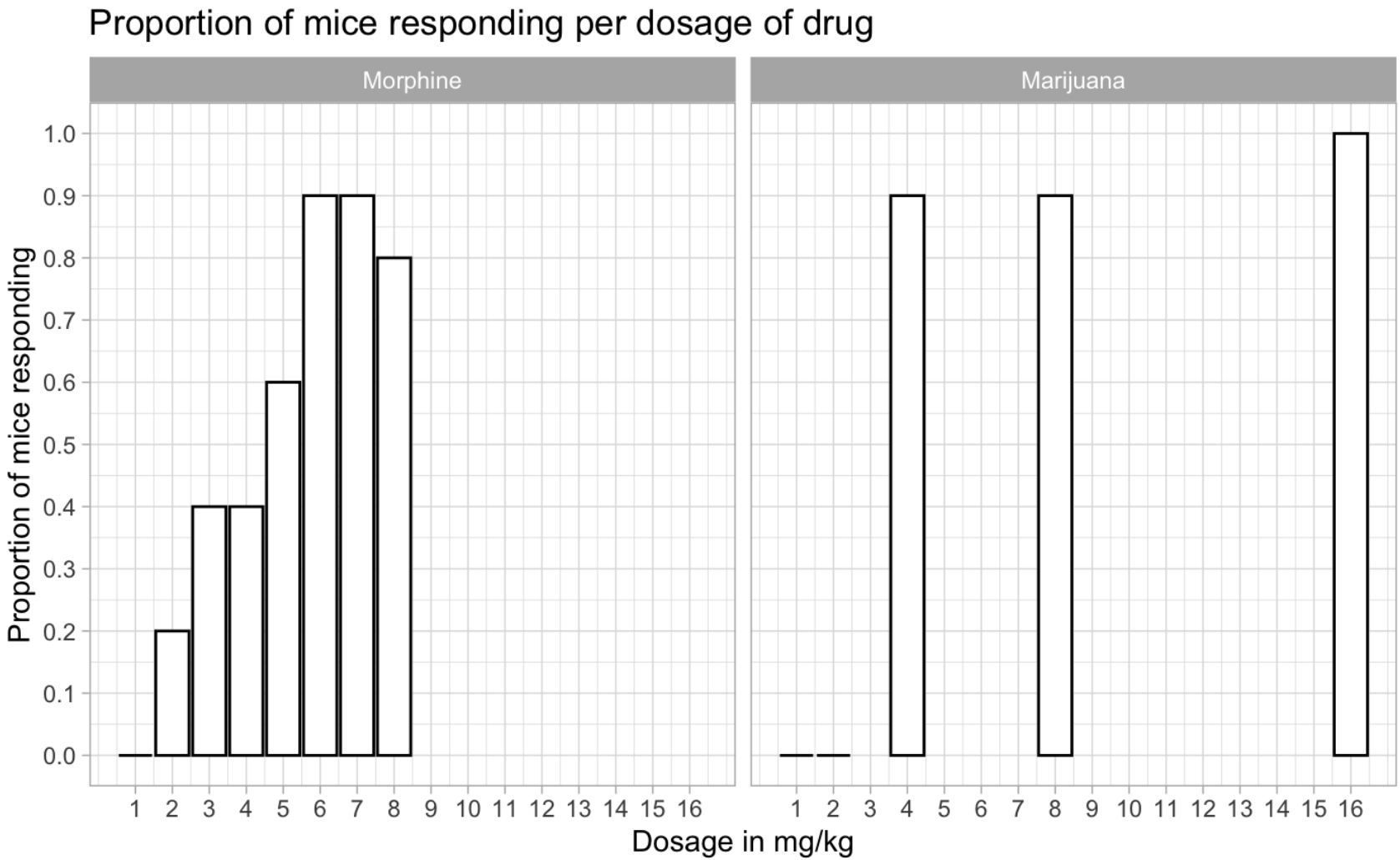
Isoboles method assumption

The ratio between dosages of morphine and marijuana when they give the same efficiency level is constant.

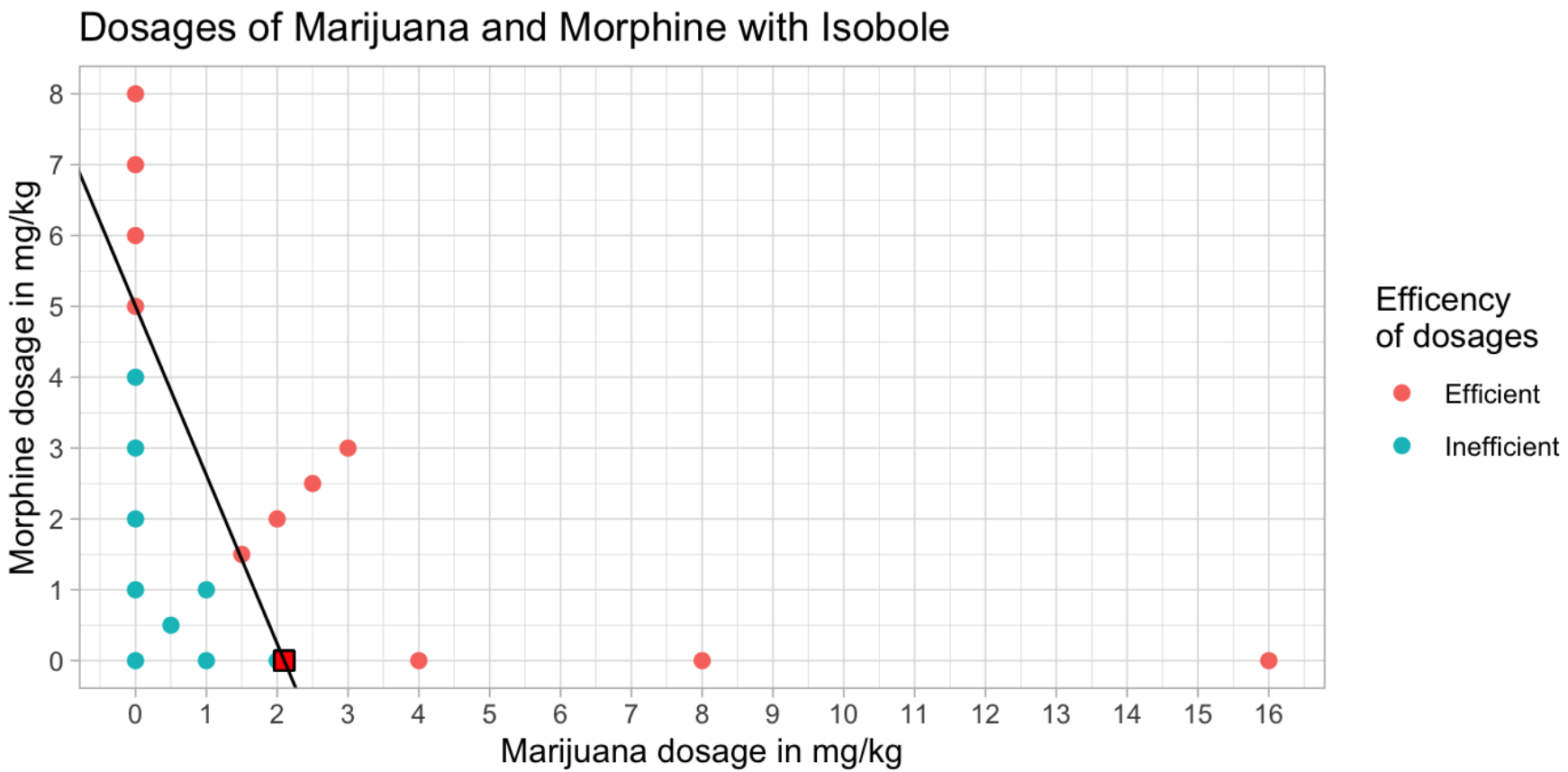

Dosages of Marijuana and Morphine vs Efficiency
Morphine
Marijuana
Dosage in mg/kg
16
12
8
4
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
Efficiency

- Only two common efficiency levels, 0.0 and 0.9
- This is not enough to verify the assumption for this experiment.
- This weakness is due to dosage choices for marijuana.
- However, the linear isobole method is used in multiple experiments which are extremely similar.

Dosage choices for marijuana



- The choice of dosages for marijuana does not allow for precise exploration of the minimal efficient dosage.
- A better minimal efficient dosage could be found between 2.0 and 4.0 mg/kg.
- This could change the isobole in a drastic way, making it more strict towards the synergic dosages.


Dosages of Marijuana and Morphine with Isobole
Morphine dosage in mg/kg
0
1
2
3
4
5
6
7
8
Marijuana dosage in mg/kg
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
Efficency of dosages
Efficient
Inefficient

Recommendations

- ✓ **Complete the experiment with trials for at least 3 or 4 dosages of marijuana between 2.0 and 4.0 mg/kg.**
- ✓ Experiment with more dosages of morphine between 4.0 and 5.0 mg/kg.
- ✓ As of now, the best minimal efficient dosage is 1.5 mg/kg of marijuana and morphine combined.