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# Climate change impact modelling needs to include cross-sectoral interactions

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## Abstract

Climate change impact assessments often apply models of individual sectors such as agriculture, forestry and water use without considering interactions between these sectors. This is likely to lead to misrepresentation of impacts, and consequently to poor decisions about climate adaptation. However, no published research assesses the differences between impacts simulated by single sector and integrated models. Here we compare 14 indicators derived from a set of impact models run within single sector and integrated frameworks across a range of climate and socio-economic scenarios in Europe. We show that single sector studies misrepresent the spatial pattern, direction and magnitude of most impacts because they omit the complex interdependencies within human and environmental systems. The discrepancies are particularly pronounced for indicators such as food production and water exploitation which are highly influenced by other sectors through changes in demand, land suitability and resource competition. Furthermore, the discrepancies are greater under different socio-economic scenarios than different climate scenarios, and at the sub-regional rather than Europe-wide scale.

The Intergovernmental Panel on Climate Change (IPCC) has stated the need and importance of undertaking integrated, cross-sectoral assessments of climate change impacts in order to account for the indirect effects of climate change. This is a prerequisite for any type of comprehensive climate impact assessment that aims to inform adaptation or mitigation planning. However, as the IPCC Fifth Assessment report (AR5)<sup>1</sup> states: *“Little information is available on integrated and cross-sectoral climate change impacts in Europe, as the impact studies typically describe a single sector [...]. This is a major barrier in developing successful evidence-based adaptation strategies that are cost-effective.”* Impact assessments that do not account for cross-sectoral interactions have the potential to misrepresent impacts and thus, the need or otherwise for adaptive action. This

misrepresentation is likely to be reflected in an over- or under-estimation of impacts with the magnitude of these differences varying through time and across space.

Impacts resulting from future socio-economic change have been shown, in some cases, to be greater than impacts based on future climate change alone<sup>2,3,4,5,6</sup>. It is often through the socio-economic drivers that cross-sectoral impacts become evident, as policy effects in one sector can have indirect effects in others, and these effects are lost in single sector studies. Given this situation, it is perhaps surprising that many impact studies continue with a single sector emphasis, e.g. the Agricultural Model Intercomparison and Improvement Project (AgMIP)<sup>7</sup> and most of the studies reported in the IPCC AR5<sup>8,9</sup>. This could in part be due to the predominantly disciplinary nature of climate impacts research, whereas multidisciplinary and transdisciplinary approaches are essential for understanding the complexity of cross-sectoral interactions. However, whilst the importance of integrated approaches is becoming recognised<sup>10,11</sup>, it could also be related to a lack of knowledge about the significance of such cross-sectoral interactions for understanding the magnitude and spatial distribution of future impacts, as no studies have evaluated the discrepancies arising from a single sector approach.

Here we demonstrate the importance of an integrated approach to climate change impact assessment by comparing indicators derived from a common set of impact models run within a single sector framework and an integrated framework that accounts for cross-sectoral interactions. The analysis uses the CLIMSAVE Integrated Assessment Platform (IAP<sup>12,13</sup>), which links models of agriculture, forestry, urban growth, land use, water resources, flooding and biodiversity. The IAP is a spatially-explicit modelling platform that operates on a 10 x 10 minute grid for the countries of the European Union plus Norway and Switzerland. It has been thoroughly validated (Supplementary Table 1) and widely applied in climate change impact<sup>2,4,6,14,15</sup>, adaptation<sup>16</sup> and vulnerability<sup>17</sup> assessment, in robust policy analysis<sup>18</sup>, and has been tested extensively through model sensitivity<sup>19</sup>

and uncertainty analysis<sup>20,21</sup>. It was applied with and without coupling of the individual sectoral models for a number of scenario experiments for the 2050s that included different SRES emissions scenarios<sup>22</sup>, climate change models<sup>23</sup> and the socio-economic storylines underlying the SRES scenarios<sup>22</sup>. Differences between the single sector and integrated model results for a number of impact indicators were determined and analysed statistically for significance of difference.

### **Climate change impacts from single sector studies**

We recognise that climate change impact results are strongly influenced by the choice of impact model<sup>24</sup>, even when models have been well validated against historical observations. Thus, we have carried out a benchmarking exercise (see Supplementary Table 2 and associated text) to test the pertinence of the single sector models within the IAP with respect to current knowledge from the literature, by demonstrating that the models can replicate the types of European impact results summarised in the “Europe” chapter of the IPCC AR5<sup>1</sup> for a range of indicators.

### **Europe-wide model outcomes differences**

Differences between impact indicators from running the IAP as a set of stand-alone single sector models and a fully coupled, integrated model including cross-sectoral interactions are shown in Figure 1 for all the scenario experiments. The figure shows the proportion of indicators that are identical across the two modelling approaches, but does not show the magnitude of difference between individual indicators. There are clear differences between the single sector and integrated models and across the scenarios, ranging from 3% (little agreement) to 100% (total agreement). In general, the greatest differences are seen for food provision and water exploitation, and the smallest differences for the forest-related indicators and urban land cover. This reflects the degree of influence that other sectors have on each indicator. For example, in the integrated model

allocation of land for urban development is assumed to take precedence over other land uses, and so other sectors do not affect urban development and there are no differences between the single sector and integrated model outcomes for this indicator. Forestry indicators differ little between scenarios, as it is assumed that current tree species do not adapt to climate change. Hence, there is little expansion in forestry in either the single sector or integrated model runs as tree species become stressed with climate change and forestry struggles to compete with other land uses based on profitability.

Conversely, food production and water exploitation are highly influenced by other sectors through changes in demand, land suitability and competition for land. For example, the agricultural area needed for food production is affected by widespread (albeit small) changes in urbanisation as well as changes in the frequency of flooding which alters the land suitability for different farming activities. Furthermore, changes in irrigation water availability influence the selection of irrigated and non-irrigated crops grown in an area which in turn affects agricultural profitability and food production. Similarly, water exploitation has significant influences from changes in irrigation use in the agricultural sector as well as competing demands for water from domestic and other sectors as reflected by changing population patterns in the urban model. Biodiversity indicators vary between single sector and integrated models, depending on how land use changes from other sectors, such as agriculture and forestry, affect the habitats for particular species.

Figure 1 also shows how the differences between single sector and integrated models vary depending on the type of scenario. Around half of the indicator-scenario combinations have more than 80% identical values with different climate models (39 out of 70 [54%]; panel 1 in Figure 1) and different emissions scenarios (32 out of 56 [57%]; panel 2) when socio-economic conditions remain unchanged. However, only 21 out of 56 [38%] (panel 3) and 26 of 70 [37%] (panel 4) of indicator-scenario combinations have more than 80% identical values with the future socio-economic

scenarios. This is because changes in socio-economic drivers, such as population, GDP, food imports and technology, stimulate greater interactions between the sectoral models. For example, under the A2 socio-economic scenario an increase in population combined with decreases in food imports and negligible improvements in technology leads to substantial land use change as agriculture expands in order to meet European food demand which in turn leads to large scale reductions in forest area, increases in irrigation usage and water exploitation, and greater vulnerability for species which are not associated with agricultural habitats. None of these cross-sectoral interactions which are stimulated by the socio-economic drivers are captured in the single sector stand-alone model runs.

The selection of climate model or emissions scenario has only a relatively minor effect on the variability of differences between single sector and integrated models for an individual impact indicator. This is shown by the relatively small range of values in the first and second panels of Figure 1. In contrast, uncertainties related to the inclusion of socio-economic scenarios with different climate models and emission scenarios result in a much greater range of differences between single sector and integrated models with seven indicators having ranges greater than 15% and four (food provision, unmanaged land, arable land and intensive agriculture) having ranges of more than 30% across the different socio-economic scenarios (panel 3).

Figure 2 shows the magnitude of the under- and over-estimation of the single sector models with respect to the integrated model across the range of scenarios. The differences arising from the range of climate models (5 models) and emissions scenarios (4 scenarios) are reflected as minimum and maximum values. Very few impact indicators have little or no difference (urban being the exception), so almost all of the indicators are to some extent over- or under-estimated by the single sector models. Some indicators have extremely high differences (over 100%) such as the water exploitation index and arable biodiversity. Other indicators have relatively large differences (25-100%) such as irrigation, forest biodiversity and people flooded. There are some differences between the climate,

socio-economic and emissions scenarios for some, but not all, of the indicators. The results taken as a whole provide evidence in support of the basic premise presented here that single sector models misrepresent the full range of possible climate change impacts, and that this is reflected in both over- and under-estimation of impacts.

### **Sub-regional model outcomes differences**

The IAP is a spatially-explicit model and so we are able to compare differences between the single sector and integrated models geographically. Figure 3 highlights how the inclusion of cross-sectoral interactions leads to very different spatial patterns for the indicators. The scenario (SRES A2) illustrated represents a hot, wet climate for Europe with a large increase in population (+25%), a decrease in food imports (-10%) and no water savings from technological or behavioural change (Supplementary Table 3). The integrated model run shows greater water exploitation values across river basins in much of southern, central and eastern Europe than the single sector model runs due to a simulated increase in irrigation which becomes profitable due to the pressure of meeting food demand with a higher population and reduced imports. However, the spatial distribution of food production varies between the single sector and integrated model runs. The single sector runs show higher levels of irrigated food production in much of Spain and central to eastern Europe, whilst in the integrated run food production increases to a greater extent in Fennoscandia where irrigation is not needed but climate conditions have improved sufficiently to support more agricultural production. This leads to both a reduction in forest cover in northern Europe as forests are converted to agriculture and an increase in forest production in areas where food production has decreased. In southern Spain, this reduced need for irrigation leads to less water exploitation compared to the single sector model outputs.



Figure 4 shows sub-regional differences between single sector and integrated model runs across a wider range of scenarios. All of the European sub-regions show large differences in both directions both with and without socio-economic changes. This arises because, as demonstrated in Figure 3, each combination of climate and socio-economic scenario leads to complex cross-sectoral interactions that the single sector models cannot take into account. For example, irrigation use changes significantly by scenario in the integrated model because it is able to adapt to dynamic changes in crop yields and water availability in a way that the single sector models, with static inputs for these variables, cannot. As such under the GFCM21 climate model with baseline socio-economic parameters, irrigation is shown to have both positive and negative differences (>5%) from the single sector models in the northern, Atlantic and continental regions depending on the SRES emissions scenario. The changing profitability of irrigated crops has indirect impacts on many of the land use indicators such as arable land, intensive agriculture, extensive grassland and unmanaged land which also show both positive and negative differences (>5%) depending on the scenario. Under the IPCM4 climate model, where changes in precipitation are less marked, there are fewer differences between the single sector and integrated models, but some differences remain, particularly for food production and irrigation (Supplementary Figure 1).

Sub-regional differences between single sector and integrated models greatly increase when socio-economic changes are included in the scenarios shown in Figure 4 as drivers such as population growth, GDP, technological change (for water savings, irrigation efficiency and crop yields) and behavioural change (for water savings and dietary preferences) have differential influences on the sectoral models in the modelling chain. Increasing or decreasing water savings in the water model, for example, can significantly alter the amount of water available for irrigation, modifying the profitability of agriculture and the spatial pattern of irrigation use, and resulting in indirect impacts for other land uses (such as forestry) and for biodiversity depending on the habitats these land uses support.

## Benefits of integrated modelling approaches

Comparing differences in the IAP indicators when computed using a single sector vs integrated modelling approach highlights the implications of relying solely on sectoral models (Figure 5). For most indicators, both single sector and integrated models project the same direction of change relative to baseline. However, there are cases where the direction of change projected by single sector models is the opposite of that projected for the integrated model; this includes water exploitation, people flooded, arable land, intensive agriculture, extensive grassland, carbon storage and biodiversity. This is particularly noticeable for agricultural indicators, where maximum European levels of arable, intensive agriculture and extensive agriculture are 62-72% of baseline levels in the single sector models and 118-156% of baseline values in the integrated model where cross-sectoral interactions are taken into consideration. This reflects the considerable changes in land use needed to meet food demand when additional pressures are placed on the agricultural system from other sectors, e.g. losses of high quality agricultural land due to urban expansion, changes in water availability for irrigation and changes in timber demand from forestry.

Furthermore, significant differences in the magnitude of change are apparent even when the single sector and integrated models agree on the direction of change relative to baseline. Of the maximum and minimum differences shown in Figure 5, 60% are more than  $\pm 10\%_{BL}$  and 24% are more than  $\pm 50\%_{BL}$  (see Figure 5 for explanation of units). Of those differences which are greater than  $\pm 10\%$ , 82% show that the indicator value from the integrated model is higher than from the single sector models.

The range of projections across the scenarios (between the minimum and maximum scenario values) also expands as a result of model integration. Across all indicator-region combinations the

integrated model shows an increase in range of more than 10%<sub>BL</sub> in 58% of cases, and more than 50%<sub>BL</sub> in 27%. The variables with the greatest increase in range are the agricultural land use classes (intensive agriculture, extensive grassland, arable), abandoned land and irrigation, all of which have range expansions of more than 50%<sub>BL</sub> in multiple regions; the water exploitation index also increases in range by more than 50%<sub>BL</sub> in the continental region. Contractions in projection ranges due to model integration are less common with no indicators showing reductions in range across all regions. However, the range of outcomes for food provision and carbon storage reduce by more than 25%<sub>BL</sub> in a number of regions, particularly the northern and alpine regions.

The IAP takes a largely linear approach to data transfer within the impact model chain that only includes limited feedbacks when applied within a single simulation round and assumes that the consequences of cross-sectoral interactions manifest themselves within the 30-year timeslice. Given these limitations and the widely recognised uncertainty within impact models themselves, a different modelling approach would inevitably generate results that differ in the magnitude and spatial patterns of the impact differences reported here. However, we believe that such modelling differences would not change the overall system understanding which is gained by the *a priori* implementation of cross-sectoral interactions directly within modelling frameworks, rather than considering cross-sectoral interactions as an *a posteriori* discussion of sectoral impact results<sup>25</sup>.

Single sector impact models that ignore the complex interdependencies present in human and environmental systems will generally inadequately represent the spatial patterns, directions and magnitudes of most indicators of climate-sensitive impacts. Whilst the choice of climate model and emissions scenario introduces differences in impact results between single sector and integrated impact models, these effects are dwarfed by the consequences of highly uncertain future socio-economic change. These arise due to the high sensitivity of some elements of environmental systems to socio-economic drivers (such as rural land use allocation), and the way in which such

effects propagate through the dependencies within an integrated modelling system. Furthermore, this analysis has demonstrated quantitatively for the first time the uncertainty arising from a siloed, single sector perspective and cautions against the use of outputs from sectoral models to inform adaptation policy. This highlights the importance of developing adaptation plans that are robust to changes in climate and socio-economic pathways and that take account of cross-sectoral interactions.

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### **Author Contributions**

PAH conceived the idea for the study; all authors designed the study; RWD undertook the model runs and data analysis; all authors contributed towards the writing of the paper.

### **Competing Financial Interests statement**

The authors declare no competing financial interests

### **Figure Legends**

Figure 1: Comparison of single sector and integrated model outcomes: proportion of dataset where identical values are found between the single sector and integrated models. Black squares reflect the range (R) of data: ■ = R>5%, ■■ = R>15%, ■■■ = R>30%.

Figure 2: Difference due to (a) under-estimation and (b) over-estimation of single sector models compared to integrated models. The values are based on the total of all positive (a) or negative (b) differences summed across all grid cells and standardised relative to the baseline value.

Figure 3: Spatial patterns in differences between single sector and integrated models for an indicative scenario (GFCM21 climate model combined with SRES A2 emissions and socio-economic changes). Both positive and negative differences are presented relative to baseline levels at the grid-cell scale.

Figure 4: Differences between single sector and integrated model impact indicators for the five European regions used in the Europe Chapter of the IPCC AR5<sup>1</sup>. Positive differences indicate that the integrated model produces higher values than single sector models; negative differences indicate that the single sector model values are greater. Both positive and negative differences are presented relative to baseline levels at the regional scale. Based on the GFCM21 climate model combined with baseline or future socio-economics.

Figure 5: Differences between single sector and integrated models by region with respect to the minimum and maximum European summed IAP results for each indicator. Colour indicates the agreement between model types in terms of the direction of change; triangle and arrow symbols indicate the magnitude of difference between the single sector and integrated models. All units are % change from baseline (%<sub>BL</sub>): a value that changes from 100% to 75% of baseline would be -25%<sub>BL</sub>.



### Climate change impact modelling needs to include cross-sectoral interactions

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#### The CLIMSAVE IAP

The CLIMSAVE<sup>1</sup> IAP<sup>12,13</sup> integrates a suite of sectoral models, including agriculture, forests, biodiversity, flooding, water resources and urban development to simulate the cross-sectoral effects of different climate and socio-economic scenarios across Europe. To facilitate the cross-sectoral model linkages and to reduce model run-time within the web-based software environment, a meta-modelling approach was used whereby computationally efficient or reduced-form models that emulate the performance of more complex models were developed (see Supplementary Table 1 for further details). Each meta-model has been calibrated and validated against either historical observations or the outputs from the validated complex models – see citations within Supplementary Table 1. In addition, all of the meta-models have undergone comprehensive sensitivity analysis<sup>19</sup> and uncertainty analysis<sup>20,21</sup> and been reported within integrated cross-sectoral impact, adaptation and vulnerability assessments<sup>4,14,17</sup>.

The IAP is based on a web Client / Server architecture that uses both server-based (i.e. remote) and client-based (i.e. the user's PC) computing solutions on the web<sup>13,26</sup>. The models are hard-linked (i.e. there is no off-line coupling) within the server-side software environment. Supplementary Figure 2 schematically illustrates the model inter-linkages showing the key model variables that are passed between models. The interactions take place as part of a hierarchical model chain. The exception is

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<sup>1</sup> Climate change Integrated Methodology for cross-Sectoral Adaptation and Vulnerability in Europe

for the interaction between agriculture and water availability for irrigation, whereby the maximum allowed water withdrawals for irrigation (from the Water Availability model) constrains the Rural Land Allocation model, the results from which determine the actual irrigation water use which then feeds into the Water Use model and the assessment of overall water exploitation. This approach was chosen to keep runtime to a minimum within the web-based system. However, within the broader concept of the IAP, the user of the IAP provides the feedback mechanism, as undesirable impacts in a 'downstream' sector (for example, on habitats) can be used to trigger changes in the input values for earlier models within the following model run.

As an example of these inter-linkages, the Rural Land Allocation Model optimises the spatial rural land allocation to meet scenario food demand by selecting between intensive agriculture (arable or dairying), extensive agriculture (grass-based livestock systems), managed forest, unmanaged forest or unmanaged land based on profit maximisation under a range of constraints. Land use selection is constrained by land that is unavailable for agricultural use due to urbanisation (from the Urban Model), frequency of flooding (from the Flooding Model), protected area status or physical constraints (e.g. soil depth). Crops are selected on the basis of relative profitability, which depends on their simulated rainfed and irrigated yields (from the Crop Yield Model) and the maximum allowed water withdrawals for irrigation in a given river basin (from the Water Availability Model). Managed versus unmanaged forest is determined on the basis of whether simulated timber yields (from the Forestry Model) for the baseline tree species achieve sufficient profit. Capital, people and trade flows are treated exogenously within the IAP, so that GDP, population and food imports are specified as scenario variables. Crop and livestock production prices are not set but are iteratively adjusted within each IAP run so that farm profits allow sufficient agricultural area to meet the required European food demand. As European food demand increases, imports decrease and/or agri-environment measures (such as buffer strips, set-aside, etc.) increase, then simulated food

prices will increase. Outputs of simulated irrigation usage and habitat availability are passed from the Rural Land Allocation to the Water Use and Biodiversity models, respectively.

The Platform operates at a spatial resolution of 10 arcmin x 10 arcmin (approximately 16km x 16km in Europe) for all Member States of the European Union minus Croatia (EU27) plus Norway and Switzerland. The IAP runs for three independent thirty year time slices: baseline (1961-90 climate with 2010 socio-economics), 2020s and 2050s. Hence, there is no time-dependence in the model runs. It produces outputs of both sector-based impact indicators and ecosystem services (see examples in Supplementary Table 1) taking account of cross-sectoral trade-offs in order to link climate change impacts directly to human well-being. Fourteen impact indicators were selected to cover different sectors/ecosystem services for the comparison of single sector vs integrated model runs: food provision, area of arable land (including set-aside), area of intensive agriculture, area of extensive grassland, area of managed forest, area of unmanaged forest, area of unmanaged land, carbon storage, water exploitation index, irrigation use, number of people flooded (1% annual probability), arable biodiversity, forest biodiversity and urban land area (see Supplementary Table 4 for further details).

### **Scenario experiments**

The IAP was run for 41 scenario experiments for the 2050s to explore how uncertainties arising from climate and socio-economic change affect the differences between the single sector and integrated model runs. These scenario experiments included:

- one baseline scenario using current socio-economic conditions (2010) and climate data (1961-1990 average);

- 20 climate change-only scenarios based on four SRES emissions scenarios (A1, A2, B1, B2)<sup>22</sup> combined with five climate models (MPEH5, CSMK3, HadGEM, GFCM21 and IPCM4) selected to represent as much uncertainty as possible arising from between-GCM differences<sup>21</sup>. Projections of Europe-wide average temperature change range from 1.5 to 4°C in the 2050s, whilst precipitation changes range from increases of between 1 and 11% in winter and decreases of between 4 and 25% in summer;
- 20 combined climate and socio-economic scenarios where socio-economic conditions are changed from baseline based on the same four SRES scenario storylines, downscaled to Europe using information from previous studies <sup>27,28</sup> and expert opinion (see Supplementary Table 3 for details of the quantified values used for different socio-economic inputs to the IAP).

Both the single sector and integrated models were run for the climate change scenarios alone and for combined climate and socio-economic scenarios to determine the differences due to different drivers of change.

The climate and socio-economic scenarios were applied separately as well as combined to tease apart the roles that the different drivers play in single sector and integrated model outcomes. The climate change scenarios were run with baseline socio-economics (rather than simulating future 2050s socio-economics with baseline climate) to be consistent with current understanding of climate change. Our focus therefore allows us to understand how the inclusion of socio-economic changes modifies the impacts associated with climate change.

## **Statistical analysis**

Grid cell differences between single sector and integrated models were calculated by subtracting the two variables from one another. The number of cells with a difference value greater than zero was calculated and used for Figure 1 in the main article. Statistical similarity in the spatial distribution of the impact indicators between the single sector and integrated models has been assessed using the concordance coefficient (Supplementary Figure 3). Concordance metrics were calculated by applying Lin's equation<sup>29</sup> to the single sector and integrated datasets for a given scenario experiment providing a measure which reflects the goodness of fit to a 1:1 line. Those indicators heavily influenced by the inputs of other models, reflecting cross-sectoral interactions, generally show lower concordance: food provision, water exploitation, carbon storage, irrigation and extensive grassland all show notable differences (concordance correlation coefficient,  $\rho_c < 0.95$ ) under at least one scenario combination. Concordance values vary between climate models reflecting the influence of the different spatial patterns of temperature and precipitation change. The socio-economic scenarios introduce further significant spatial differences between the single sector and integrated models when compared with differences for the same climate model under current socio-economic conditions.

The total difference between single sector and integrated models was calculated for each scenario pair and the total over-estimation (positive difference) and under-estimation (negative difference) calculated by summing all difference values greater than and less than zero, respectively. These differences were then standardised by re-calculating them as the proportion of the total value for the same indicator from the baseline scenario experiment (Figure 2 in main article). A regional analysis of the differences was performed in a similar manner by calculating total differences for each IPCC region and standardising them relative to the total value for the region for the same indicator from the baseline scenario experiment (Figure 4 in the main article).

The total value and change from baseline were calculated for each indicator and scenario experiment for the whole of Europe and each of the five IPCC European regions (Supplementary Figure 4) for both the single sector and integrated model runs. The maximum and minimum extreme values of each indicator for each scale were identified from the totals and standardised by calculating each as a proportion of the baseline value (Figure 5 in main article). Direction relative to baseline was identified using this proportional value; if the value was greater than or equal to 101% of baseline it was classified as an increase, and if less than or equal to 99% of baseline classified as a decrease. Direction was compared between the single sector and integrated models, and each indicator was classified in terms of whether the directions were different or the same, and if so, in which direction. The range was calculated for each indicator at each spatial scale by subtracting the minimum indicator value (as a proportion of baseline) of any scenario from the equivalent maximum. This was performed for both the single sector and integrated models and the difference in range resulting from model integration was calculated by subtracting the single sector range from the integrated range. The scenario with the highest value and the scenario with the lowest value, compared to baseline, was also computed for each of the five IPCC regions and compared for the single sector and integrated models for the IPCC indicators given in Table 1 (main article) (see Supplementary Table 5). This provides an overview of how results in the IPCC Europe chapter might differ from what has been reported if the studies had taken account of cross-sectoral interactions.

## References for the Online Methods Section

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